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CLINICAL EXPERIENCES IN THE USE OF DETERMINATIONS OF BLOOD IODINE

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In the study of disease of the endocrine glands it is extremely important to be able to determine with accuracy the amounts of hormones present in the body. The results of assays of blood and urine for the amount of estrogenic hormone serve as indexes of the production of ovarian follicular hormone.[1] Assay for testicular hormone in the urine is of considerable assistance in the diagnosis of hypogonadism in the male,[2] and the estimation of the amount of the gonadotropic hormone in the blood and urine by various methods gives a means of estimating the activity of the pituitary gland.[3] The value for blood iodine may be used as a direct indication of the activity of the thyroid gland.

Various methods have been described by which determinations of blood iodine may be made. Modifications of the von Fellenberg technic [4] have been used successfully, but the method requires experience and technical skill and is so time-consuming that it is impracticable for routine clinical use. In 1934 a new method was described by D. Roy McCullagh,[5] which is accurate, simpler and more rapid. The results reported

From the Cleveland Clinic.

1. Frank, R. T., and Goldberger, M. A.: Clinical Application of the Female Sex Hormone Test, New York State J. Med. **29**:671 (June 1) 1929. Kurzrok, R.: Estimation of Estrin and Follicle-Stimulating Hormone in Urine as Index of Therapy in Menstrual Dysfunction, Endocrinology **16**:361 (July-Aug.) 1932.

2. McCullagh, E. P.; McCullagh, D. R., and Hicken, N. F.: Diagnosis and Treatment of Hypogonadism in the Male, Endocrinology **17**:49 (Jan.-Feb.) 1933.

3. Fluhmann, C. F.: Anterior Pituitary Hormone in the Blood During Pregnancy: Preliminary Report, J. A. M. A. **92**:1744 (May 25) 1929.

4. von Fellenberg, T.: Die Bestimmung kleinster Jodmengen in organischen Materialen, Biochem. Ztschr. **224**:170, 1930.

5. McCullagh, D. Roy: A New Method for the Determination of Iodine, J. Biol. Chem. **107**:35 (Oct.) 1934.

here were selected from approximately two hundred determinations of blood iodine which were made in clinical cases by the use of this procedure.

The normal value for blood iodine is approximately 10 micrograms per hundred cubic centimeters of blood; therefore 10 cc. of blood must be examined to determine the presence of as small an amount of iodine as 1 microgram (0.001 mg.). Each iodine level given in the accompanying tables was determined after at least two tests had been made.

Table 1 shows examples of blood iodine levels of patients with diseases which were not related to the thyroid gland. In case 2 some

TABLE 1.—*Blood Iodine Values for Patients Without Thyroid Disease*

Case	Sex	Diagnosis	Basal Metabolic Rate, Percentage	Blood Iodine, Micrograms per 100 Cc.
1	M	Prostatic hypertrophy	−9, −4	9.5
2	M	Prostatic hypertrophy	−14, −16, −27	7.2
3	M	Mongolism	Impossible	9.1
4	M	Mental deficiency	−16	10.3
5	F	Dyspituitarism	−4, −12	9.7
6	M	Angina pectoris	−10	9.8
7	F	Psychosis	Impossible	10.5
8	F	Psychosis	−17, −9	11.1
9	M	Arterial hypertension	+7	13.2
10	F	Neurocirculatory asthenia	+4	12.5
			Average	10.2

TABLE 2.—*Effect of Violent Exercise on the Amount of Iodine in the Blood*

Time in Relation to Exercise	Blood Pressure	Pulse Rate	Respiratory Rate	Blood Iodine, Micrograms per 100 Cc.
Before	110/80	64	21	8.0
Immediately after	135/85	148	40	9.2
15 minutes after	115/82	104	23	5.3
45 minutes after	95/75	88	20	6.3
2 hours after	110/90	76	21	6.8

degree of hypothyroidism may have been present. The average level in these patients is comparable to that usually seen in normal persons.

Table 2 shows the effect of strenuous exercise for ten minutes on the blood iodine level of a normal man. The fact that a slight rise was followed by a subsequent fall to a subnormal level suggests that the increase in blood flow caused a temporary "flushing out" of iodine from the thyroid gland. During experiments such as this, the metabolic rate rose in one case to 353 per cent above the normal basal rate. This fact indicates that a knowledge of the basal condition is not necessary when determination of blood iodine is being made to exclude the presence of hyperthyroidism, but it does show that strenuous exercise may cause distinct variation in blood iodine levels.

In table 3 there are shown some blood iodine levels in cases of active hyperthyroidism which were observed clinically. It will be observed that the height of the basal metabolic rate and that of the blood iodine level are not always proportionate to the increased metabolism. In these cases the iodine levels vary from 11.1 to 49.8 micrograms per hundred cubic centimeters of blood.

Table 4 is a tabulation of data from cases in which a clinical diagnosis of hypothyroidism was made because of the presence of typical

TABLE 3.—*Blood Iodine Values in Cases of Active Hyperthyroidism*

Case	Basal Metabolic Rate, Percentage	Blood Iodine, Micrograms per 100 Cc.
1	+34	25.6
2	+58	42.4
3	+70	20.9
4	+23	24.2
5	+70	11.1
6	+57	21.5
7	+60	23.4
8	+51	38.9
9	....	49.8
10	+53	38.7

TABLE 4.—*Blood Iodine Values in the Presence of Hypothyroidism*

Case	Sex	Basal Metabolic Rate, Percentage	Blood Cholesterol, Mg. per 100 Cc.	Blood Iodine, Micrograms per 100 Cc.
1	F	—27	222	8.7
2*	F	—22	224	7.7
3	M	—20	217	6.7
4	M	—16, —14	210	6.6
5	F	—21, —22	230	6.3
6	F	—26, —27	...	7.5
7	F	—30	...	7.4
8†	F	—20	277	10.8
9	F	—24, —15	204	6.0
10	F	—30	164	7.6
			Average	7.5

* Progressive exophthalmos.

† Thyroid extract had been administered orally until two weeks before the estimation of blood iodine was made.

symptoms and signs, a low basal metabolic rate and, in most instances, a relatively high blood cholesterol level. Cases in which hypometabolism was present but in which there was no other evidence of thyroid deficiency were not included in this table. It is interesting to note that in case 2 severe progressive exophthalmos was present, which continued to increase after operation. This is the only case in this group in which studies of the blood iodine were made after operation. In case 8 desiccated thyroid had been taken by mouth until two weeks before the estimation of blood iodine was made. The average blood iodine level in this group of cases was 25 per cent lower than that noted in the cases of non-

thyroid diseases. This appears to indicate that the test is of considerably less value in the diagnosis of hypothyroidism than in the diagnosis of hyperthyroidism, especially in individual cases, since the total extent of the change is relatively small. This fact, however, does not alter its usefulness in the study of groups of patients who have hypothyroidism.

Table 5 includes cases of hypometabolism in which there was no clinical evidence of thyroid disease. In cases 2 and 3 the patients were markedly emaciated and had amenorrhea. After careful study no plausible explanation for their symptoms was shown other than hypopituitarism. Although the value for blood iodine was slightly low in case 1 it scarcely seems proportionate to the low metabolic rate. In cases 5 and 6, normal iodine levels were noted.

High blood iodine levels have been reported to accompany infections and leukemia, and Curtis [6] found high blood iodine levels in certain patients in whom arterial hypertension was present. The administration

TABLE 5.—*Blood Iodine Values in Cases of Hypometabolism Not Related to the Thyroid Gland*

Case	Diagnosis	Basal Metabolic Rate, Percentage	Blood Iodine, Micrograms per 100 Cc.
1	Narcolepsy	—24	7.0, 6.0
2	Pituitary cachexia	—42, —40	7.1
3	Pituitary cachexia	—26, —38	11.2
4	Pituitary basophilism	—18, —19	6.6
5	Exhaustion, sexual neurosis	—22	9.7
6	Prepubertal hypogonadism	—16, —27	12.1

of iodine promptly raises the blood iodine level, and the preoperative use of aqueous solution of iodine U.S.P. (Lugol's solution) produces a level of from 500 to 600 micrograms per hundred cubic centimeters. In some cases, high blood iodine levels have been found to be inconsistent with the clinical data. In all except one of these cases, the patient was in the hospital, where much iodine is used, and we believe there had been inadvertent contamination.

It has been much more common in our cases thus far to observe high basal metabolic rates associated with normal blood iodine levels than to observe normal metabolic rates associated with high blood iodine levels. Table 6 gives two examples of cases of hypertension in which this is true. In both these instances hyperthyroidism was suspected. In cases 3 and 4 in this table, it is a matter of conjecture whether the metastatic carcinoma caused an elevation of the metabolic rate by producing the effect of an arteriovenous aneurysm or whether the rise in

6. Curtis, G. M., and Cole, Vera V.: The Blood Iodine in Thyroid Disease. Tr. Am. A. Study Goiter, 1934, p. 142.

the basal metabolic rate was produced by the absorption of toxins. The normal blood iodine level suggests, however, that a diagnosis of hyperthyroidism is made too frequently when malignant disease of the thyroid gland is present. A similar relationship is seen in case 5—an instance of aneurysm of the internal carotid artery. No explanation is offered for the completely normal iodine level in the case of acromegaly.

The determination of blood iodine is sometimes of distinct value in the differential diagnosis of disease of the thyroid gland. This was shown in the cases of arterial hypertension previously cited. In case 1 in table 7 hyperthyroidism was suspected because of clinical evidence

TABLE 6.—*Blood Iodine Values in Nonthyroid Hypermetabolism in Which There Was No Evidence of Thyroid Disease*

Case	Sex	Diagnosis	Basal Metabolic Rate, Percentage	Blood Iodine, Micrograms per 100 Cc.
1	F	Hypertension (230/165)	+55, +58	7.0
2	F	Hypertension (190/140)	+53, +36	8.1
3	F	Malignant goiter; metastases	+28, +41	10.3
4	F	Malignant goiter; metastases	+29, +26	6.1, 7.4
5	M	Aneurysm of internal carotid artery	+22, +17	9.5, 9.6
6	F	Acromegaly; goiter	+20, +26	9.0, 9.0

TABLE 7.—*Blood Iodine Values as an Aid in Differential Diagnosis*

Case	Disease Suspected	Diagnosis	Basal Metabolic Rate, Percentage	Blood Iodine, Micrograms per 100 Cc.
1	Hyperthyroidism	Neurocirculatory asthenia	+20, −5	9.9, 9.0
2	Cretinism	Congenital mental deficiency	−16	10.3
3	Cretinism	Cerebral injury	....	13.0
4	Hyperthyroidism	Neurocirculatory asthenia	−7, −8	12.0
5	? Hyperthyroidism	Encephalitis	....	11.7
6	Hyperthyroidism	Hypo-ovarianism	+12, +12	7.1
7	Hyperthyroidism	Simple goiter	+21, −12	12.5

and because the basal metabolic rate on the first determination was + 20 per cent. The diagnosis was revised, however, when the blood iodine level was repeatedly found to be normal. Subsequently the basal metabolic rate was —5 per cent. A similar occurrence was seen in case 7, in which the patient was a very active, rather excitable girl, 12 years of age, who had a tendency to tachycardia, and in whom the results of the first metabolism test confused the clinical picture further, since hyperthyroidism had been suspected. In cases 2 and 3 a diagnosis of cretinism was ruled out because of clinical findings and because normal epiphyseal growth was revealed by the roentgenogram. Normal values for blood cholesterol and for blood iodine formed good corroborative evidence. In case 3, the fact is demonstrated that the blood iodine level may help to exclude the presence of hyperactivity of the thyroid

gland in cases in which it is impossible to determine the basal metabolic rate in young children. By means of determinations of blood iodine the possible diagnosis of hyperthyroidism was excluded in case 5, also, when cooperation could not be obtained for making a test of metabolism. In case 6, symptoms associated with the menopause simulated those of hyperthyroidism, but the correct diagnosis was made after the blood iodine was measured.

SUMMARY

From a study of these cases, it is indicated that in Cleveland the blood iodine levels of normal adults and of patients who have diseases which are not associated with the thyroid gland range from approximately 8 to 12 micrograms per hundred cubic centimeters.

The blood iodine level is very high in cases in which iodine medication has been instituted. Exercise has little influence in raising the level of blood iodine, but strenuous exertion may have a temporarily depressing effect.

Under controlled conditions the blood iodine level is proportionate to thyroid activity in most cases, the change in the level, however, being relatively greater in persons with hyperthyroidism than in those with hypothyroidism.

Determinations of blood iodine are of value in the differential diagnosis of hyperthyroidism.

EXPERIMENTAL DIABETES INSIPIDUS IN THE MONKEY

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The experimental production of diabetes insipidus in a large series of cats has been reported, and the various phases of the problem of the etiology of this condition have been discussed in a series of recent publications.[1] It is sufficient for the present to state that polyuria of long duration has always been found, in our experience, in association with lesions of the hypothalamus placed so as to interrupt the bundle of unmyelinated fibers which runs from the nucleus supra-opticus down the infundibular stalk into the pars posterior of the hypophysis. In these cases atrophy of the supra-optic nucleus and of the pars nervosa has been a striking feature of the changes observed at autopsy. The development and course of the polyuria in cats are characteristic. Usually, although not always, the operation is followed by the immediate onset of a transient polyuria, which subsides after from one to four days. From eight to fifteen days after operation (the so-called latent period) the permanent phase of the polyuria develops, and it continues with some fluctuation, and in varying degrees of intensity in different subjects, until the animal is killed. This polyuria can be controlled by the administration of pitressin and can be greatly influenced by the feeding of thyroid substance and sodium chloride.[1c]

So far as we know, the production of experimental diabetes insipidus in monkeys has not been reported, although it is desirable that this animal should be used on account of its closer relationship to the human species. Therefore, a group of macaques was operated on, and the subsequent occurrence of diabetes insipidus in two of them is reported here.

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1. (*a*) Fisher, C.; Ingram, W. R., and Ranson, S. W.: The Relation of the Hypothalamico-Hypophyseal System to Diabetes Insipidus, Arch. Neurol. & Psychiat. **34**:124 (July) 1935. (*b*) Fisher, C.; Ingram, W. R.; Hare, W. K., and Ranson, S. W.: The Degeneration of the Supra-Optico-Hypophyseal System in Diabetes Insipidus, Anat. Rec. **63**:29 (Aug. 25) 1935. (*c*) Fisher, C., and Ingram, W. R.: The Effect of the Feeding of Thyroid Extract or Salt and of Thyroidectomy on the Fluid Exchange of Cats with Diabetes Insipidus, to be published.

METHODS

Young specimens of Macaca mulatta weighing between 2 and 3 Kg. were used. The lesions in the hypothalamus were produced electrolytically with the aid of the Horsley-Clarke stereotaxic instrument. After operation the animals were placed in metabolism cages, and the output of urine and the consumption of water were measured daily. The food consisted of fresh vegetables and fruit in as nearly constant quantities as possible, with the addition of 120 cc. of milk each day. Trouble was experienced in the early experiments because of the tendency of the monkeys to spill their water. This was largely obviated by the use of reservoir jars, which were placed above the cages and which fed water as needed into small cups anchored to the wall and floor of the cage. Indications of spilling could then be checked by examination of a small quantity of talcum powder sprinkled on the drain pan just beneath the water cup. The specific gravity of the urine as determined with an ordinary urinometer was recorded each day.

RESULTS

Diabetes insipidus developed in two of the eight monkeys used in these experiments. One of these (MD 9) showed a decided increase in the average output of urine, the average volume before operation being 266 cc., which corresponds closely with the average for the seven normal monkeys, and that after operation being 749 cc. (table). The other (MD 5) showed more moderate polyuria, the output of urine after operation averaging 485 cc. The remaining monkeys showed no significant increase; on the other hand, four of them had a diminished volume of urine after operation, while their intake of water was markedly reduced. The results in general are summarized in the table, but it should be pointed out that the figures for the intake of water for the first four animals must be considered to be only approximate, owing to difficulties of measurement during the period of observation. The discrepancies between the output of urine and the intake of water may be considered to be made up by the consumption of milk and in some cases by the amount of water contained in the food. Accurate measurement of the consumption of milk was, for various reasons, not possible; usually from 50 to 120 cc. was taken. Also the average figures for MD 5 and MD 9 do not represent quite the full degree of the polyuria, as the output of urine during the latent period between operation and the onset of the polyuria was included, as was also the output during the two days when no water was given. The average daily output of urine during the permanent phase of the polyuria, excluding the two days of deprivation of water, was 577 cc. for MD 5 and 851 cc. for MD 9.

The course of the polyuria shown by MD 5 and MD 9 is of some interest.

In the case of MD 5 there was no evident transient phase, the output of urine immediately after operation remaining within the normal range. However, the

consumption of water dropped to zero on the fourth, fifth and sixth postoperative days. The polyuria developed rather suddenly on the fourteenth day, when the volume of urine increased from 250 cc. to 500 cc., and the intake of water jumped from 225 cc. to 475 cc. Some occult change may have preceded this sudden change in actual volume, since the specific gravity was unusually low (1.006) for two days before the onset of the polyuria. During the latent period the output of urine averaged 271 cc., with a specific gravity of 1.009, and the consumption of water averaged 153 cc. During the permanent phase the average daily output of urine exclusive of that on the two days on which no water was given, was 577 cc., with a specific gravity of 1.004, and the consumption of water averaged 487 cc. Attempts to control the polyuria in this animal with pitressin were disappointing, but it was later found that the preparation we were using was relatively inactive. Deprivation of water reduced the output of urine from 620 cc. to 235 cc., and 135 cc. on successive days.

Average Output of Urine

Monkey	Average Output of Urine Before Operation, Cc.	Average Specific Gravity Before Operation	Average Output of Urine After Operation, Cc.	Average Specific Gravity After Operation	Average Water Intake Before Operation, Cc.	Average Water Intake After Operation, Cc.	Days Observed After Operation
			Monkeys Without Polyuria*				
MD 1	216	1.011	246	1.012	140	103	15
MD 2	227	1.012	163	1.011	104	20 (?)	15
MD 3	273	1.011	161	1.014	203 (?)	12	21
MD 4	298	1.009	149	1.014	268 (?)	8	20
MD 10	207	1.013	298	1.011	94	56	39
MD 11	307	1.009	255	1.009	179	96	25
			Monkeys With Polyuria				
MD 5	...	.....	485†	1.005	...	412†	58
MD 9	266	1.011	749†	1.005	160	585†	85

* Seven normal monkeys showed an average output of urine of 256 cc., with a specific gravity of 1.011.

† Including the latent period and two days when no water was given and periods when pitressin was administered.

MD 9 gave clear evidence of transient polyuria. On the three days following operation the volumes of urine were 540, 570 and 500 cc., with specific gravities of 1.005, 1.005 and 1.007, respectively. The quantities of water consumed during these three days were 475, 550 and 250 cc. The output of urine then declined to a low normal level, reaching 100 cc. (specific gravity 1.022) on the seventh postoperative day. The consumption of water also dropped, reaching zero on the eleventh and twelfth days. The onset of the permanent phase was more gradual in this instance, but on the thirteenth day the volume of urine increased from 375 cc. to 470 cc., and the consumption of water rose from 0 to 335 cc. The exchange of water then rose rapidly to a high level, which persisted during the period of survival of the animal. The average daily output of urine during the permanent phase, exclusive of the two days on which no water was given, was 851 cc.; the specific gravity was 1.0048, and the average consumption of water was 664 cc. The peak output of urine was 1,220 cc., and volumes over a liter were observed on seventeen occasions. On the two days during which the animal was deprived of water the output of urine dropped from 850 cc. to 590 cc. and 200 cc. on successive days. The averages include several days during which pitressin was administered. The matter of the effect of pitressin deserves special mention at this point.

On several occasions pitressin, which was later found to be deficient in activity, was injected. This had a relatively slight effect on the polyuria, the output of urine at one time dropping from 780 to 525 cc. The striking thing, however, was the marked rebound rise which followed the cessation of injection; on the day following the administration of pitressin the volume of urine rose from 525 to 1,150 cc. Shortly before MD 9 was killed an active preparation of pitressin was obtained.[2] This was found to have a marked but evanescent effect. On January 30, 0.66 cc. of pitressin was injected subcutaneously in two doses, 0.33 cc. at 10:30 a. m. and 0.33 cc. at 4 p. m. During the period from 10:30 a. m. to 9 p. m. only 150 cc. of urine was excreted, but during the night the output of urine returned to a very high level, and 560 cc. was produced. On January 31, 1 cc. of pitressin was given in three doses of 0.33 cc. at 9:30 a. m., 1:30 p. m. and 4:45 p. m. From 9:30 a. m. to 5 p. m. only 25 cc. of urine was excreted and no water was drunk, but between 5 p. m. on January 31 and 9 a. m. on February 1, 375 cc. (specific gravity 1.010) was produced. During the next twenty-four hours the volume of urine was 850 cc. (specific gravity 1.005). It will be seen that when the animal was under the influence of these small doses of pitressin it became practically anuric but that during the night, presumably as the effects of the drug passed off, a fair rate of excretion of urine was resumed. This night sample had a relatively high specific gravity, however, and it was probably not until the next day that the polyuria was in full swing again.

ANATOMIC FINDINGS

Examination of the sectioned brain stems of the monkeys of this series showed that in MD 5 and MD 9 the lesions were placed so as to interrupt the supra-optico-hypophyseal tract, with concomitant atrophic changes in the supra-optic nuclei and in the pars posterior of the hypophysis. In the animals in which the results were negative, the lesions either did not affect this system or encroached on it so slightly that very little atrophy occurred in the supra-optic nuclei and the posterior lobe of the pituitary. It is significant, however, that in these animals lesions in the hypothalamus which differed little from those in MD 5 and MD 9 but which did not interrupt the supra-optico-hypophyseal tract did not produce polyuria. Furthermore, in a large group of monkeys used for other experiments, lesions have been placed throughout the extent of the lateral hypothalamic area and in the medial and lateral portions of the posterior hypothalamic region, including the region of the mamillary bodies, and no tendency to polyuria has been observed.

A brief statement as to the anatomy of the hypothalamico-hypophyseal system in the normal monkey may facilitate the description of the experimentally produced lesions.

The Hypothalamico-Hypophyseal Fiber System in the Monkey.—The nucleus supra-opticus in the monkey lies just rostral and dorsal to the

2. This preparation was supplied by Dr. Oliver Kamm, of Parke, Davis & Co.

beginning of the optic tract, with a medial and ventral component caudal to the chiasm. In sagittal sections of the hypothalamus stained by the pyridine silver method this nucleus is seen to give rise to a rather heavy bundle of fibers which passes caudomedially over the dorsal surface of the optic chiasm and also apparently to send a number of fibers directly into the dorsal portion of the latter. The more superficial bundle becomes heavier as it passes medioventrally, presumably as fibers from other portions of the hypothalamus, including the ventromedial portion of the supra-optic nucleus, join it. A number of fibers which come from some point dorsal and medial to the supra-optic nucleus also join the tract—these may arise in the paraventricular, or filiform, nucleus (Roussy and Mosinger [3]). The exact origin of the fibers which enter the tract from areas caudal to the supra-optic nucleus could not be determined with exactitude; apparently most of them arise in the ventromedial hypothalamic nucleus, with comparatively few coming from the more posterior nuclei. As the fibers approach the ventral surface of the brain stem they turn almost directly mediad and pass into the walls and floor of the infundibulum, converging toward the pituitary stalk mediocaudally. Near the midline a heavy component appears coursing down the anterior wall of the infundibulum; these fibers appear to come from the dorsocaudal part of the chiasm. If such is the case, it is logical to assume that they are the continuations of the fibers which seemed to pass from the supra-optic nucleus directly into the chiasm. In this connection one may recall the remark of Papez and Aronson [4] à propos the apparent connection of the supra-optic nucleus with fibers of the optic system. Greving [5] also described a supra-optico-thalamic tract which was said to rise in the optic chiasm and to pass through the supra-optic nucleus on its way to the thalamus. However, with the preparations available at present one cannot exclude the possibility that this rostromedial component may be formed by the condensation of scattered fibers which have taken a more dorsal course from the supra-optic or other nuclei. A possible pathway through the chiasm, however, is indicated by a broken line in figure 4. Once gathered in the infundibulum, the fibers pass as a very heavy tract down the pituitary stalk into the pars nervosa, where they divide and scatter into an enormously complex meshwork which spreads among characteristic groups or islets of cells which are presumably identical with the pituicytes described

3. Roussy, G., and Mosinger, M.: Rapports anatomiques de l'hypothalamus et de l'hypophyse, Compt. rend. Soc. de biol. **112**:557, 1933.

4. Papez, J. W., and Aronson, L. R.: Thalamic Nuclei of Pithecus (Macacus) Rhesus: I. Ventral Thalamus, Arch. Neurol. & Psychiat. **32**:1 (July) 1934.

5. Greving, R.: Die Fasersysteme des Hypothalamus, in Müller, L. R.: Lebensnerven und Lebenstriebe, ed. 3, Berlin, Julius Springer, 1931, p. 150.

by Bucy.[6] The islet structure is characteristic of the normal pars nervosa. We are unable to say whether any of these fibers enter the pars intermedia in the monkey, although small numbers of them have been said to do so in man (Bucy [6]) and in the cat (Fisher et al.[1b]). Figure 3 illustrates the appearance of the normal supra-optico-hypophyseal tract in the infundibular stalk of the monkey.

It will be seen that hypothalamic lesions designed to interrupt the supra-optico-hypophyseal tract must cover a rather wide area and that those placed at the opening of the infundibulum, where the fibers converge, have the best chance of producing complete destruction of this system (fig. 4).

It has been pointed out [1b] that the innervation of the posterior lobe of the pituitary gland has two main constituents, these together being called the hypothalamic-hypophyseal tract. The first of these arises from the supra-optic nuclei and is designated the supra-optico-hypophyseal tract; the other comes from cell groups farther caudad and may be called the tubero-hypophyseal tract. Figure 4 is a diagrammatic representation of the hypothalamico-hypophyseal system in the monkey.

The Lesions in Monkeys in Which Diabetes Insipidus Did Not Develop.—MD 1: Cross-sections stained with cresyl violet showed the lesions to be placed well caudal to the beginning of the stalk, bilaterally, affecting the ventromedial hypothalamic nuclei, extending caudad to destroy most of the premamillary region and destroying the right mamillary body almost completely.

MD 2: Cross-sections stained with cresyl violet showed the lesions to be situated bilaterally, on the ventral surface of the hypothalamus (fig. 1 A) just caudal to the pituitary stalk, extending caudad into the ventral portion of the premamillary area and terminating just ventral to the rostral border of the mamillary bodies. The supra-optic nuclei, pituitary stalk and hypophysis were normal in appearance.

MD 3: Cross-sections showed that the bilateral lesions encroached slightly on the caudal border of the chiasm and extended caudad on the ventral surface of the hypothalamus, meeting in the midline just above the infundibulum. Farther caudad the tuber cinereum proper and the mamillary bodies were largely destroyed and the right lateral hypothalamic area was encroached on, but the supramamillary area remained intact. The dorsal wall of the infundibular recess was thin, but the ventral part of the stalk was well developed. There was a moderate increase in the number of cell nuclei in the pars nervosa of the pituitary body, indicating some involvement of the tubero-hypophyseal fibers. The supra-optic and filiform nuclei were large and well developed and were of normal cell structure, indicating integrity of their fibers, although it was not clear how the latter escaped at least partial destruction.

6. Bucy, P. C.: The Hypophysis Cerebri, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, p. 765.

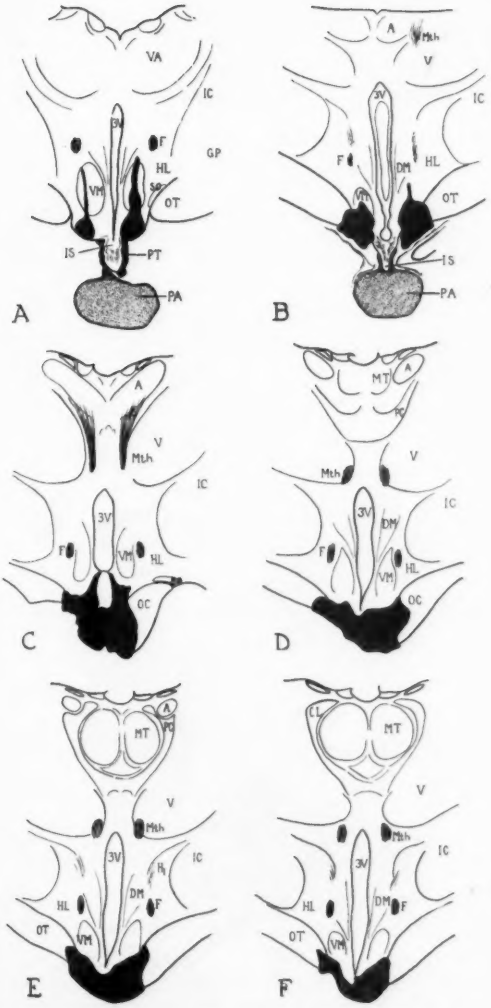

Fig. 1.—*A*, drawing showing the location of lesions in MD 2, in which polyuria did not develop. The lesions are indicated by solid black. *B*, drawing showing the location of lesions in MD 4, in which polyuria did not develop. The lesions are indicated by solid black. *C* to *F*, drawings showing the location of lesions in MD 5, in which moderate polyuria developed. The lesions are indicated in solid black.

The abbreviations used in figure 1 and in the other illustrations are as follows: *A*, anterior nucleus of the thalamus; *AC*, anterior commissure; *BV*, blood vessel; *CL*, nucleus centralis lateralis; *DM*, nucleus hypothalamicus dorsomedialis; *F*, fornix; *Fi*, persisting fibers of tubero-hypophyseal tract; H_1, field of Forel; *HL*, lateral hypothalamic area; *IC*, internal capsule; *IS*, infundibular stalk; *L*, lesion; *M*, mamillary body; *MH*, medial hypothalamic region; *MT*, medial nucleus of thalamus; *Mth*, mamillothalamic tract; *OC*, optic chiasm; *OT*, optic tract; *P*, preoptic area; *PA*, pars anterior of hypophysis; *PC*, nucleus paracentralis; *PP*, pars posterior of hypophysis; *PT*, pars tuberalis of hypophysis; *SO*, nucleus supra-opticus; *SHT*, supra-optico-hypophyseal tract; *TC*, tuber cinereum; *THT*, tubero-hypophyseal tract; *V*, nucleus ventralis of thalamus; *VM*, nucleus hypothalamicus ventromedialis.

MD 4: Cross-sections showed that the rostral extent of the lesions affected the ventral surface of the optic chiasm. There was a small area of softening just dorsal to the chiasm in the midline. Caudally the lesions lay at the ventral surface of the hypothalamus just dorsal to the beginning of the infundibulum but did not meet in the midline, leaving room for the passage of supra-optico-hypophyseal fibers (fig. 1 B). The ventromedial hypothalamic nuclei were severely

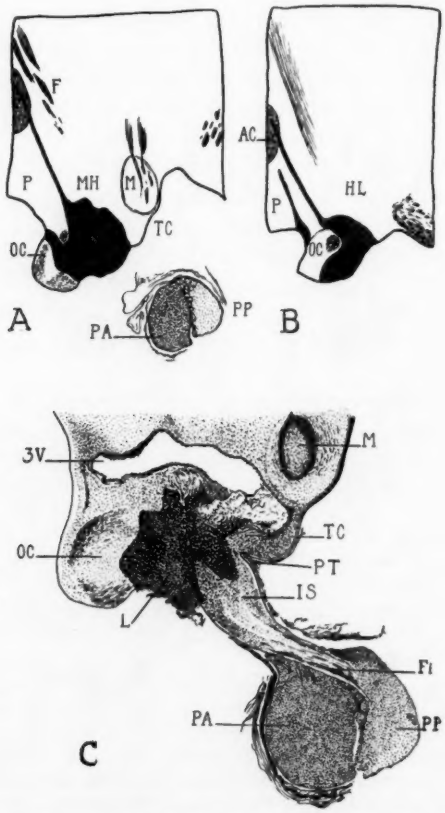

Fig. 2.—*A*, drawing showing the location of lesions on the left side of the brain in MD 9, in which polyuria developed. Sagittal sections prepared with pyridine silver. *B*, drawing showing the lesions on the right side of the brain in MD 9. *C*, drawing of sagittal section of the hypothalamus and hypophysis of MD 9 stained with pyridine silver, showing the lesion and degeneration of the supra-optico-hypophyseal tract. Compare with figure 3 which shows a normal tract.

damaged, and there was slight damage to the premamillary area. The supra-optic nuclei were large and well developed. The pituitary stalk was well developed but

showed slight gliosis. The posterior lobe of the hypophysis was of normal size and showed a relatively slight increase in the number of cell nuclei.

MD 10: Cross-sections showed that on the left side the lesions lay just caudal to the chiasm, destroying the ventromedial portion of the supra-optic nucleus and extending dorsad as far as the tip of the third ventricle. The pars tuberalis was partially destroyed on the left side, and the left wall of the infundibulum was damaged. The lesion extended caudad into the premamillary area. On the right side the lesions were farther from the midline and affected especially the ventral surface of the optic tract. The chief damage on this side was an area of softening (probably of vascular origin) which destroyed the lateral hypothalamic area caudal to the ventromedial component of the supra-optic nucleus and which extended dorsad into the anterior part of the dorsal thalamus and the anterior limb of the internal capsule. This damage extended caudad as far as the mamillary bodies, the right one of which was atrophic because of the inter-

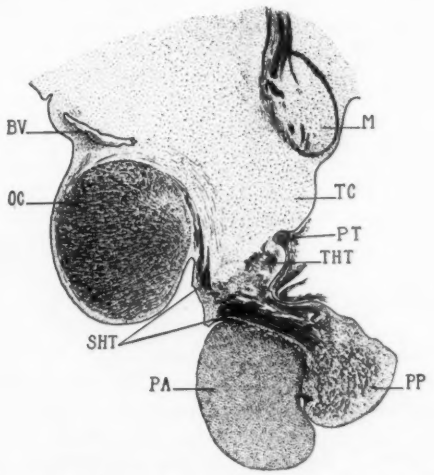

Fig. 3.—Drawing of sagittal section of hypothalamus and hypophysis prepared with pyridine silver, showing the normal hypothalamico-hypophyseal fiber system in MD 11. Compare with figure *2 C*.

ruption of the fornix and the mamillothalamic tract. The left supra-optic nucleus was atrophied; the right, especially its ventromedial component, was well developed. The posterior lobe of the pituitary gland showed a mild increase in the number of cell nuclei.

MD 11: Sagittal sections stained with pyridine silver showed the electrolytic needle to have passed clear through the diencephalon with a minimum of damage to the hypothalamus, there being no electrolytic lesions in the brain substance. Although there was a very extensive area of softening in the right dorsal thalamus and corpus striatum, the hypothalamico-hypophyseal system was unaffected and furnished a good example of the normal condition (fig. 3).

The Lesions in Monkeys with Diabetes Insipidus.—MD 5: Cross-sections stained with cresyl violet showed that the lesions extended well forward through the optic chiasm, which was largely destroyed, producing some damage dorsal to

the chiasm in the midline (figs. 1 *C* to *F*). Caudal to the chiasm the lesions extended across the midline at the ventral surface of the hypothalamus, affecting the ventral edges of the ventromedial hypothalamic nuclei, and approached the infundibulum closely without separating it completely from the hypothalamus. The rostral wall of the infundibular recess was scarred, and its ventral wall was heavily gliosed; the dorsal wall, however, was clear, indicating the presence of unmyelinated fibers. The pituitary stalk proper was heavily gliosed, except at its dorsal and lateral edges. The posterior lobe of the pituitary gland, which was smaller than normal, showed a remarkable increase in the number of cell nuclei, which rendered it so dark that the borders of the pars intermedia were hardly distinguishable. The lateral portions of the supra-optic nuclei were of relatively short extent and contained some shrunken cells and gaps indicating loss of cells; the ventromedial portions were practically absent, such cells as remained appearing shrunken. The character of the lesions and the clearness of the dorsal wall of the infundibular recess and of the upper dorsal part of the stalk indicated survival of a number of tuberohypophyseal fibers. The supra-optic fibers must have been considerably reduced in number.

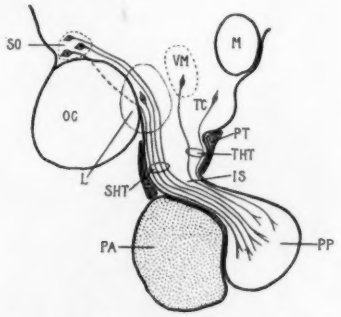

Fig. 4.—Diagram of the hypothalamico-hypophyseal fiber system of the monkey. The rings separate the supra-optico-hypophyseal tract (*SHT*) and the tuberohypophyseal tract (*THT*). The possible course of fibers of *SHT* through the chiasm is indicated by a broken line. The area enclosed by the finely dotted line indicates the approximate location of the lesions which produce diabetes insipidus in the monkey. The single cell just behind the chiasm represents the ventromedial component of the supra-optic nucleus.

MD 9: Sagittal sections stained with pyridine silver showed the lesions to be somewhat asymmetrically placed, those on the right side being well removed from the midline and destroying the medial half of the supra-optic nucleus and involving a large part of the optic chiasm, only a small bundle of optic fibers remaining in the optic tract. Caudally the lesion lay on the caudal edge of the chiasm (fig. 2 *B*), extending mediad close to the ventral surface of the brain, destroying the ventromedial portion of the supra-optic nucleus and encroaching on the ventromedial hypothalamic nucleus. The lateral hypothalamic area was also damaged at the level of the chiasm. No supra-optico-hypophyseal fibers could be seen arching over the degenerated chiasm or passing through the latter, although other groups of normal fibers passed over what remained of the supra-optic nucleus, which was markedly degenerated. Although supra-optic fibers were absent, a number of other fibers from the region of the tuber had accumulated.

Many of these came from the caudal portion along the ventral surface of the tuber; others came from the region of the ventromedial hypothalamic nucleus; all could be traced into the infundibulum.

The damage produced by the lesions on the other side extended mediad to the midline on the posterior border of the chiasm, destroying the ventromedial portion of the supra-optic nucleus and encroaching on the anterior wall of the infundibulum, the cavity of which contained many large cells (phagocytes or fibroblasts). This damaged area extended dorsad as far as the floor of the third ventricle to the left of the midline and ventrad encroached on the pituitary stalk, which contained a sparse scattering of fibers. Laterally the lesions were sufficiently extensive to include part of the ventromedial hypothalamic nucleus and to damage the chiasm severely (fig. 2 *A*). The latter, although atrophic (compare figs. 2 *C* and 3), contained some fibers on this side. The lesions were less extensive farther laterally but persisted in the caudal part of the chiasm and in the immediate postchiasmatic and suprachiasmatic regions. The supra-optic nucleus was atrophic, containing only shrunken, abnormal cells, and very few fibers issued from it. The pituitary stalk contained relatively few fibers, which were evidently of tuberal origin, since the supra-optic fibers were completely absent (compare figs. 2 *C* and 3). The posterior lobe of the hypophysis was somewhat decreased in size and showed a rather uniform structure, the normal islet formation and massive meshwork of fibers being absent.

The hypophysis was unaffected directly by the lesion in MD 5, the pars tuberalis, the pars intermedia and the pars anterior appearing normal in the sections stained with cresyl violet. There was some damage to the pars tuberalis in MD 9, but so far as could be determined in the preparations stained with pyridine silver the pars anterior and the pars intermedia were normal.

COMMENT

The results described show that the syndrome of diabetes insipidus can be produced experimentally in the monkey by a technic similar to that used in the cat. The polyuria thus produced follows a course similar to that in the cat, the onset of the permanent phase of the increase in water exchange being preceded by a latent period during which polyuria of transient character may occur. The etiology of the latter is still in doubt, although it has been suggested that it may be due to irritative processes consecutive to the placing of the lesion (Fisher, Ingram and Ranson,[1a] Ingram and Barris[7]). The occurrence of a latent period is also of interest, further evidence for such a period being found in the protocols of other experimenters who have succeeded in producing diabetes insipidus in animals and one clinical case of diabetes insipidus of traumatic origin having been reported in which there was a latent period of twelve days before the development of the polyuria (Ciminata[8]).

The most interesting thing in relation to the experimental production of polyuria is the uniform involvement of the supra-optico-

7. Ingram, W. R., and Barris, R. W.: Diuresis Associated with Direct Stimulation of the Hypophysis, Endocrinology **19**:432 (July-Aug.) 1935.

8. Ciminata, A.: Sulla regolazione idrica e salina nell'uomo, in rapporte al diabete insipido, Fisiol. e med. **2**:641, 1931.

hypophyseal system in all our subjects, which now comprise some thirty cats besides the two monkeys. A relatively complete or very severe destruction of this system is essential, for it has been found that unilateral or partial damage is without result in cats and monkeys. There is apparently some correlation between the intensity of the polyuria and the amount of involvement, beyond a certain level, of the supra-optico-hypophyseal system, in certain subjects at least. The intense polyuria in MD 9 was associated with complete destruction of the tract and with marked atrophy of the supra-optic nucleus. In MD 5, which had a more moderate volume of urine, while there was noteworthy atrophy of the nucleus, it was not comparable with that in MD 9, indicating the escape of some fibers. The participation of this system in the regulation of water metabolism is not illogical when one recalls the numerous clinical cases in which diabetes insipidus has been consecutive to destruction of the posterior lobe of the hypophysis and the fact that extracts of this portion of the pituitary are effective in controlling the polyuria. If one considers a normal innervation of the posterior lobe to be necessary for the production or release of substances influencing the water metabolism of the body, the interruption of this innervation can then be held to produce a deficiency which is responsible for the excessive exchange of water. This idea has been advanced by Greving [9] on theoretical grounds as a partial explanation of the phenomenon, after the original suggestion of Kary,[10] and a neurohormonal hypothesis has been adopted by Roussy and Mosinger,[11] although in reports of earlier work Camus, Roussy and Le Grand [12] expressed the view that the hypothalamus alone is involved, without participation of the pituitary. Support for Greving's suggestion is found in the work of Broers,[13] who found it possible to produce polyuria in dogs by destruction of the supra-optic nuclei or by interruption of the infundibular stalk. From the standpoint of direct glandular intervention, Richter [14] recently pro-

9. Greving, R.: Zwischenhirn-Hypophysensystem, in Müller, L. R.: Lebensnerven und Lebenstriebe, Berlin, Julius Springer, 1931, p. 188.

10. Kary, C.: Pathologisch-anatomische und experimentelle Untersuchungen zur Frage des Diabetes insipidus und der Beziehungen zwischen Tuber cinereum und Hypophyse, Virchows Arch. f. path. Anat. **252**:734, 1924.

11. Roussy, G., and Mosinger, M.: Le tuber cinereum et son rôle dans les principales fonctions du métabolisme: Métabolisme de l'eau, des glucides et des lipides, Ann. de méd. **33**:301, 1933.

12. Camus, J.; Roussy, G., and Le Grand, A.: Etude anatomo-pathologique des lésions expérimentales provoquant le syndrome polyurique et le syndrome adiposo-génital chez le chien, Compt. rend. Soc. de biol. **86**:1070, 1922.

13. Broers, H.: Experimentele Diabetes Insipidus, Inaug. Dissert., Utrecht, Kemink en Zoon, 1932.

14. Richter, C. P.: Experimental Diabetes Insipidus: Its Relation to the Anterior and Posterior Lobes of the Hypophysis, Am. J. Physiol. **110**:439, 1934.

duced polyuria in a large number of rats by complete removal of the posterior lobe of the pituitary gland, the occurrence of the polyuria apparently being conditioned by the persistence of at least a major part of the anterior lobe in attachment to the brain. Other evidence can be adduced by a study of the older literature, in which permanent polyuria in animals is reported to have been associated with separation or compression of the pituitary stalk, detachment or atrophy of the posterior lobe or lesions in the infundibular or preinfundibular portion of the hypothalamus. It is, perhaps, not out of place to suggest that removal of the posterior lobe of the pituitary gland must be carried out with great care, as it has been found that relatively small remnants of this structure are sufficient to prevent the occurrence of polyuria, provided they remain in connection with the infundibular stalk (Fisher, Ingram, Hare and Ranson [1b]). Our finding of atrophy and an increased number of cell nuclei of the posterior lobe of the pituitary gland finds some parallel in the clinical findings of Davison and Selby,[15] who reported gliosis of the posterior lobe in a case of mild diabetes insipidus, and of Kraus [16] who mentioned a case in which the posterior lobe was rich in nuclei.

Numerous cases in which complete removal of the hypophysis has not been followed by polyuria necessitate still further explanation, however. These have led to the suggestion of von Hann [17] that the presence of active tissue of the anterior lobe of the hypophysis is a necessary prerequisite to the development of diabetes insipidus. Richter's [14] work supported this idea, and cases have been described in the literature in which diabetes insipidus has disappeared as a growing neoplasm has encroached on the pars anterior. The outstanding contrary evidence is the appearance of polyuria, which is said to follow the production of hypothalamic lesions in animals from which the hypophysis apparently had been removed (Camus, Roussy and Le Grand,[11] Broers [12]). Recently Biggart [18] reported three cases of diabetes insipidus in which the condition was explained on the basis of interruption of the supra-optico-hypophyseal tract, in one by a surgical injury just behind the chiasm, in one by an adenocarcinoma which destroyed the posterior lobe and stalk and in one by encephalitis, which destroyed the supra-optic nuclei. In the third case the patient was refractory to treatment with

15. Davison, C., and Selby, N. E.: Hypothermia in Cases of Hypothalamic Lesions, Arch. Neurol. & Psychiat. **33**:570 (March) 1935.

16. Kraus, E. J.: Die morphologischen Veränderungen der menschlichen Hypophyse nach Zerstörung der Zwischenhirnbasis bzw. des Hypophysenstiels und deren Folgen, Virchows Arch. f. path. Anat. **286**:656, 1932.

17. von Hann, F.: Ueber die Bedeutung der Hypophysenveränderungen bei Diabetes Insipidus, Frankfurt. Ztschr. f. Path. **21**:337, 1918.

18. Biggart, J. H.: Diabetes Insipidus, Brain **58**:86, 1935.

posterior pituitary, a finding explained by the extensive destruction of the tuberal nuclei by the disease. It was suggested that the normal site of action of the antidiuretic hormone of the posterior lobe of the pituitary gland was on the nuclei of the posterior part of the hypothalamus—since these were destroyed, treatment with posterior pituitary was ineffective. This, however, presumes a purely nervous mechanism from this point on, and it has been found that denervation of the kidneys (Bailey and Bremer,[19] Houssay and Carulla,[20] Camus and Gournay [21]) and section of the cervical portion of the spinal cord and the vagi (Bourquin [22]) have no significant effect on polyuria in dogs. Furthermore, it would follow that extensive lesions of the region of the tuber would produce diabetes insipidus. This we hesitate to accept, since in many cats extensive damage to the posterior portion of the hypothalamus has failed to be followed by polyuria. The same is true in monkeys (MD 1, MD 2, MD 3, MD 10). Also, it has been found possible in our experience to diminish by the use of pitressin the polyuria of cats in which the lesions not only interrupted the supra-optico-hypophyseal system but extended into the posterior part of the hypothalamus. Biggart's case might perhaps be explained by assuming the polyuria to be due to an irritation accompanying the active encephalitis, so intense as to overcome the antidiuretic effects of posterior pituitary. Some support for this suggestion is found in experiments of Camus and Roussy [23] in which they found that there was an initial phase of the polyuria during which hypophyseal extracts had no marked effect and a permanent phase in which the extracts lowered the output of urine. These phases may correspond to our transient and permanent periods of polyuria.

It would perhaps be going too far at the present time to state that interruption of the supra-optico-hypophyseal system is the only factor involved in the production of diabetes insipidus, although the constant occurrence of its involvement in a large number of cases of experimental polyuria and its integrity in cases in which polyuria is not present can hardly be considered to be mere coincidence. Further factors, especially those on the positive side—the actual causes of the excessive exchange of water—await investigation.

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19. Bailey, P., and Bremer, F.: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773 (Dec.) 1921.

20. Houssay, B. A., and Carulla, J. E.: Polyurie par piqûre cérébrale chez les chiens à reins énervés, Compt. rend. Soc. de biol. **85**:1252, 1920.

21. Camus, J., and Gournay, J. J.: La polyurie tubérienne après énervation des reins, Compt. rend. Soc. de biol. **88**:694, 1923.

22. Bourquin, H.: Studies on Diabetes Insipidus: I., Am. J. Physiol. **79**:362 (Jan.) 1927.

23. Camus, J., and Roussy, G.: Diabète insipide expérimental et opothérapie hypophysaire, Compt. rend. Soc. de biol. **83**:1578, 1920.

STUDIES ON NITROGEN AND SULFUR METABOLISM IN BRIGHT'S DISEASE

VII. SULFUR CONTENT OF URINARY PROTEIN

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In a study of the nitrogenous exchange of patients with Bright's disease, it was suggested by Peters that the nonprotein nitrogen content of the urine provides more significant data than the total nitrogen content of the urine. In the course of experiments designed to test the validity of this suggestion and others, we studied the total amounts of nitrogen and sulfur and compared these figures with the values for the total nonprotein nitrogen and nonprotein sulfur in the urine of patients with albuminuria.

The difference between the total nitrogen and sulfur content of the urine as voided and that of the protein-free filtrate of the same specimen of urine gives the nitrogen and sulfur content of the protein excreted. We were struck with the low sulfur content of the protein excreted by patients with "nephrosis" and extended the investigation to include the study of other types of proteinuria.

To determine the validity of the method we carried out the following procedure:

The proteins were precipitated by heat and acetic acid. Care was taken to bring the mixture just to the boiling point and to avoid prolonged boiling. Usually 300 cc. of urine was used, to which 1 cc. of a 0.5 per cent solution of acetic acid was added if the urine was acid and more if the urine was alkaline, although almost all the specimens of urine the analyses of which are reported in this paper were acid. The mixture was brought to a boil and was filtered while hot after the precipitate was allowed to settle. It was noted that the protein in the urine of the patients with "nephrosis" formed a distinctive coagulum the character of which differed from that in the urine of other persons. Since such treatment obviously denatures the protein, it seemed desirable to check the validity of the method with protein obtained without denaturation. Therefore, a specimen of urine was dialyzed, and the protein so obtained was dried and analyzed.

In the accompanying table are shown the results of the determinations carried out by calculation of the difference between the nitrogen

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Aided by a grant from the Proctor Fund for the Study of Chronic Diseases of the Harvard University Medical School.

and sulfur content of the urine as voided and that of the protein-free filtrate, and by analysis of the precipitated protein and of the dialyzed protein. It will be seen that the results of these analyses agree with reasonable accuracy. It is therefore apparent that denaturation of the protein produced by heat coagulation does not affect the sulfur content. Consequently it seemed valid to apply the simplest method, that of determination by difference, to various conditions in which proteinuria is present.

There exist only a few analyses of human serum albumin for sulfur content, but it is generally stated that the sulfur content is approximately from 1 to 2 per cent. Since the nitrogen content is close to 16 per cent, normal serum albumin presents a nitrogen-sulfur ratio of between 8:1 and 16:1. It is evident that the protein referred to in the table bears only a remote relationship to that of normal serum albumin, at least so far as its sulfur content is concerned.

Results of Analysis of the Nitrogen and the Sulfur Content of Urinary Protein by Three Methods *

Material Analyzed	Nitrogen Content	Sulfur Content	Nitrogen-Sulfur Ratio
Urine as voided	8.33 Gm.	282 mg.	30
Protein-free urine filtrate	6.78 Gm.	276 mg.	25
Urinary protein			
By difference	1.55 Gm.	6 mg. (0.06%)	259
Coagulum (heat + acetic acid 0.5%)	80.2 mg.	0.32 mg. (0.06%)	251
By dialysis	80.5 mg.	0.35 mg. (0.07%)	230

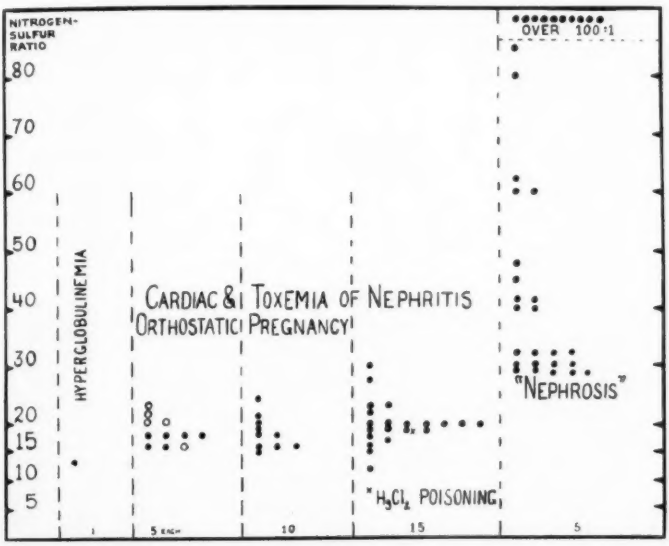
* Five-tenths gram of the dried coagulum or dialyzed protein was used for analysis. The values for the urinary protein were calculated for the twenty-four hour specimen.

In the accompanying chart are shown the results of all the analyses we have so far carried out in our preliminary survey of the problem. From this chart it is evident that patients with so-called nephrosis excrete a protein that is decidedly lower in sulfur content than the protein excreted by patients with other types of proteinuria. There appears to be a sharp dividing line between this disease and other conditions at a nitrogen-sulfur ratio of 30:1. If it is assumed that the proteinuria associated with congestive heart failure is due to increased oncotic pressure and transudation through the glomerulus into the urine, the findings for this group may be taken to represent values for serum protein. Similar considerations apply to so-called orthostatic albuminuria. The proteins excreted by patients with glomerulonephritis and with the toxemia of pregnancy are of the same order as far as the sulfur content is concerned.

Evidently only two types of patients excrete a protein of markedly different sulfur content, namely, patients with "nephrosis" and, possibly, persons with certain rare types of hyperproteinemia in which the excreted protein perhaps is related to the Bence-Jones protein.

Confirmatory evidence of these findings is available from other sources. Thus, Lang [1] demonstrated that in certain patients with renal disease there is a lowered cystine content of the serum and urinary protein. Schenck and his co-workers [2] also found lability in the amino-acid constitution of serum and organ protein. They demonstrated an inverse relationship between the cystine and the tryptophan content of various proteins, including the plasma protein.[3]

The body of evidence assembled by Lang and Schenck as to the lability of the body proteins in their amino-acid constitution is impres-



Variations in the sulfur content of urinary protein in various diseases associated with "albuminuria," expressed in terms of the nitrogen-sulfur ratio of the excreted protein. Each point represents the analysis of one specimen of urine. The small numerals at the bottom of each section of the chart indicate the number of cases studied. In the second section the results for cardiac proteinuria are indicated by solid dots and for orthostatic proteinuria by open circles.

1. Lang, K.: Die chemische Zusammensetzung der Urineiweisskörper bei Albuminurien, Arch. f. exper. Path. u. Pharmakol. **171**:73, 1933.

2. Schenck, E. G., and Kunstmann, H. K.: Ueber die Abhängigkeit des Baues der Proteine des Blutserums von den Stoffwechselvorgängen im Organismus, Ztschr. f. physiol. Chem. **215**:87, 1933.

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sive. It includes diurnal variations,[4] individual variations, modification by roentgen therapy and other agents[5] and alterations in various diseases.[6]

In the studies reported in this paper we have obtained one more evidence of such changes. The method for determination of the nitrogen-sulfur ratio of excreted protein is sufficiently simple to make it of clinical use in the differentiation of the two types of proteinuria in renal disease.

SUMMARY AND CONCLUSIONS

A simple method for determination of the nitrogen-sulfur ratio of urinary protein is described.

In cases of congestive heart failure, orthostatic albuminuria and toxemia of pregnancy the nitrogen-sulfur ratio of urinary protein averages about 20:1.

In cases of glomerulonephritis the sulfur content of the urinary protein is about the same as the sulfur content in the conditions just mentioned.

The urinary protein excreted in cases of the nephrosis syndrome has a low sulfur content. The nitrogen-sulfur ratio of this protein is above 30:1.

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HIRSUTISM, HYPERTENSION AND OBESITY ASSOCIATED WITH CARCINOMA OF THE ADRENAL CORTEX

INDETERMINATE PITUITARY ADENOMA AND SELECTIVE CHANGES IN THE BETA CELLS (BASOPHILS) OF THE HYPOPHYSIS

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Hirsutism and obesity in association with tumor of the adrenal gland [1] were first noted almost two centuries ago. Sexual precocity was added to this syndrome in 1865.[2] Finally hypertension was noted in cases of this disorder in 1897.[3] The sexual changes were studied by Glynn [4] and Gallais,[5] who in 1912 independently reviewed the literature and emphasized the relationship of those changes to the age period in which changes in the adrenal cortex occur. 1. A tumor or hyperplasia of the adrenal cortex developing during the embryonic period may be associated with pseudohermaphroditism. 2. A like condition developing during early childhood may be associated with precocious obesity with or without sexual changes or (in the male) with the "infant Hercules" type. 3. The disorder when appearing during adolescence may cause adrenal virilism (otherwise called "genito-adrenal syndrome").

Glynn was not unmindful of the interrelationship between the pituitary gland and the adrenal cortex and quoted Cushing's work on the subject. In 1912 Cushing had described the "polyglandular syn-

From the Department of Pathology, Bellevue Hospital, the Third (New York University) Medical Division, Bellevue Hospital, and the Departments of Medicine and Pathology, New York University College of Medicine.

1. Cooke, William, 1756, cited by Linser, P.: Ueber die Beziehungen zwischen Nebennieren und Körperwachsthum besonders Riesenwuchs, Beitr. z. klin. Chir. **37**:299, 1903.

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3. Neusser, E.: Die Erkrankungen der Nebennieren, in Nothnagel, C. W. H.: Specielle Pathologie und Therapie, Vienna, A. Hölder, 1897, vol. 18, pt. 3, p. 71.

4. Glynn, E. E.: The Adrenal Cortex: Its Nests and Tumours, Quart. J. Med. **5**:157, 1912.

5. Gallais, A.: Le syndrome génito-surrénal, Thèse de Paris, no. 225, 1912.

drome,"[6] but he did not then suspect what he subsequently discovered, namely, that some of these syndromes were associated with a basophil adenoma of the anterior lobe of the pituitary gland. To this interesting condition he has drawn considerable attention,[7] and he has reported 14 cases with the results of autopsy. The patients presented a clinical picture practically indistinguishable from that of adrenal virilism. It is of interest that 8 of these 14 patients showed definite hyperplasia of the adrenal cortex, and 1 patient (Dr. Anderson's) proved to have not only a basophilic adenoma of the pituitary but a "cortical adenoma or hypernephroma" of the adrenal gland.[8]

So far as we are aware,[9] this and Mathias'[10] case, to which we shall refer later, are the only recorded cases in which tumors have been found in the adrenal cortex and the anterior lobe of the pituitary gland of the same patient. We intend to record another case and to raise several questions which clinical, pathologic and hormonal studies have left unanswered.

REPORT OF A CASE

H. B., a girl aged 19, single, entered the third (New York University) medical division of the Bellevue Hospital for the second time on Dec. 27, 1933, complaining of progressive weakness, pain over the lumbar portion of the spine and lower part of the abdomen, increasing adiposity, edema of both feet and awkwardness of gait.

Previous History.—The patient was an American of Irish descent, the youngest of six living children. The mother was 64 and well; the father had died at 56 of "pleurisy." The family history was irrelevant. During childhood the patient had measles and chickenpox; at 8 years she underwent a mastoidectomy on the right side, and at 16, one on the left. Menstruation began at 12 years; the cycle was regularly established at once, recurring every thirty days; the flow was moderate and painless, lasting seven days. The patient noted a yellowish vaginal discharge in February 1931, after sexual exposure, and in November 1932 a physician found gram-negative intracellular diplococci on a smear. From that time the menstrual flow increased to thirteen days each month but remained painless. Menstruation did not occur during March and April of 1933 or during the last month of the patient's life; there was no other history of amenorrhea.

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6. Cushing, H.: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912.

7. Cushing, H.: "Dyspituitarism": Twenty Years Later, with Special Consideration of Pituitary Adenomas, Arch. Int. Med. **51**:487 (April) 1933.

8. Anderson, J.: A Case of Polyglandular Syndrome with Adrenal Hypernephroma and Adenoma of the Pituitary Gland, Glasgow M. J. **83**:178, 1915.

9. Since this report was submitted for publication, Lawrence and Zimmerman (Pituitary Basophilism: Report of a Case, Arch. Int. Med. **55**:745 [May] 1935) have recorded another case of multiple adenomas of endocrine glands in a man aged 44 who exhibited the Cushing syndrome and marked skeletal demineralization. At necropsy adenomas were found in the adrenals; another was present in the parathyroid gland, and a basophilic cell new growth was found in the anterior lobe of the pituitary.

10. Mathias, E.: Ueber Geschwülste der Nebennierenrinde mit morphogenetischen Wirkungen, Virchows Arch. f. path. Anat. **236**:446, 1922.

The present illness began in April 1933, with pain in the small of the back, edema of both feet, sudden gain in weight from 119 to 135 pounds (54 to 61.2 Kg.) and awkwardness in gait. These symptoms subsided during the next two months, and by June the patient was again able to put her shoes on easily. In September there was a recurrence of symptoms. Edema of the feet reappeared; the face became swollen and the abdomen swollen and tender. The weight rose from 135 to 150 pounds (61.2 to 68 Kg.). The patient noted large dilated veins over her breasts, thighs and abdomen. In October, she began to shave her face because of excess hair.

In November, pain in the lower portion of the abdomen became severe enough to cause the patient to come to the hospital, where she was admitted to the gynecological service. At that time she weighed 158 pounds (71.7 Kg.). Large striae were noted on the abdomen and thighs, and dilated veins were observed on the chest and abdomen. There was tenderness in both lower quadrants of the abdomen, and a vaginal discharge containing gram-negative intracellular diplococci was present. It is important to note that on admission, November 13, the blood pressure was 124 systolic and 90 diastolic, and on November 18 it was 148 systolic and 92 diastolic. Urinalysis revealed albumin (1 plus), from 8 to 10 white blood cells per high power field and urobilinogen in a 1:5 dilution. The Wassermann test was negative.

The patient was transferred to the medical service, where on November 24 the basal metabolic rate was found to be —7 per cent. The general condition improved, and on November 28 she was discharged to the endocrinology clinic, but she was sent back for hospitalization one month later. On this second admission, there were added to her complaints a cough productive of blood-streaked sputum and the appearance of purpuric areas in the skin.

Examination and Course.—The patient presented a rather striking appearance on examination (fig. 1). She was of hypersthenic habitus and appeared to be older than her age; her weight was 156½ pounds (71 Kg.) and her height 65 inches (1.65 meter). Her body had a peculiar pungent "sweaty" odor. "Pig face" best describes the appearance of the countenance, and the large chest and abdomen seemed out of proportion to the wasted upper and lower extremities. The skin was dull grayish brown, dry and coarse and bore purpuric patches varying from 5 to 25 mm. in diameter over the anterior surfaces of both thighs and extensor surfaces of both forearms. The patient did not present a plethoric appearance. Conspicuous were the long, broad symmetrical striae over the abdomen and upper portion of the thighs. These were reddish purple and were traversed here and there by dilated, dark blue tortuous veins as well as by fine, straight, bright red capillaries. Smaller striae were present over both mammae and over the proximal third of both arms at their outer aspects. Hypertrichosis was noted over the face, chin, upper lip and extensor surfaces of the legs and forearms. The hair of the head was long and dry. There was a female distribution of pubic hair. Fine dry brownish papules were distributed over the dorsa of the fingers and flexor surfaces of both wrists as well as over the outer aspects of both arms. Many comedones were seen on her greasy face. The eyes were almond-shaped; the pupils were normal. In the fundi were a few small spindle-shaped hemorrhagic areas; the arterioles were tortuous and of normal caliber. The venules looked normal and were not compressed. There was no exudate, and the margins of the disks were clear. The visual fields were normal. Both external auditory canals contained slight amounts of thick yellowish purulent discharge. Conspicuous interspaces separated the teeth, though all the molars were present.

The neck was short, and the thyroid was not palpable. Over the entire anterior surface of the chest and over the upper portion of the abdomen was noted a network of pale blue, dilated, tortuous veins. Except for the striae the mammae were normal. The lungs were clear except for dulness and diminished breathing over the lower lobe of the right lung. The heart was normal.

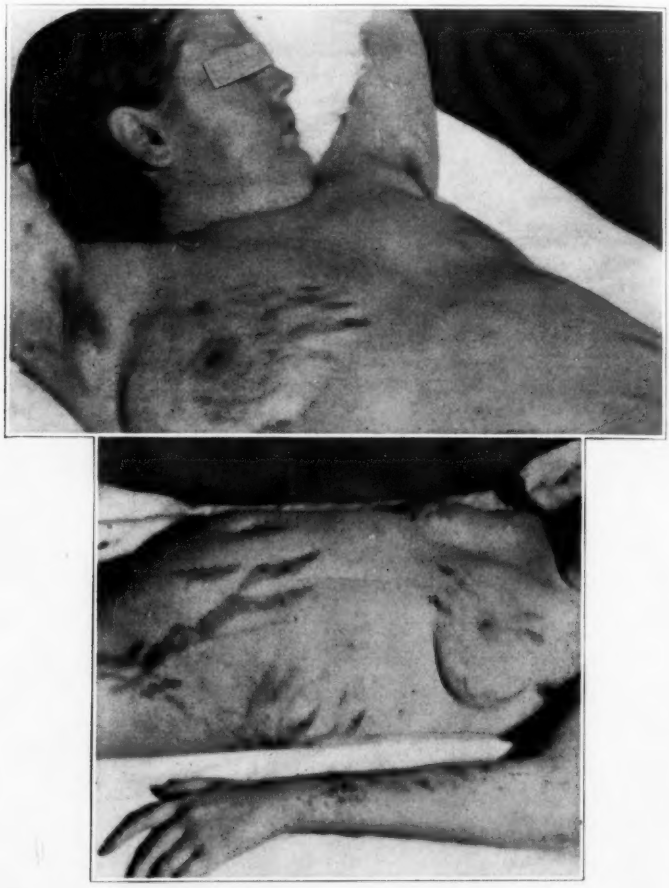

Fig. 1.—Photographs of the patient, showing hypertrichosis on the face and striae atrophicae in the axillae and over the breasts, abdomen and upper portion of the thighs. Note also the severe purpuric eruption on the forearm.

The abdomen was protuberant and bulged in the flanks. Signs of free fluid in the abdominal cavity were equivocal. The edge of the liver was palpable 6 cm. below the right costal margin and could be traced across the abdomen to a similar distance below the left costal margin; its surface was smooth. There

was considerable tenderness on light pressure over the entire abdominal wall. There was soft pitting edema (4 plus) of the dorsa of both feet and legs. The spinal column showed no deformity. Vaginal examination gave negative results except for vaginal discharge. The clitoris was of normal size. Neurologic examination gave negative results. Mentally the patient was sluggish, often noncomprehending, though her memory was fairly good both for recent and remote past events.

On admission the body temperature was 98 F. The urine was normal except for slight proteinuria. The red blood cells numbered 3,100,000; the hemoglobin content was 60 per cent, or 7.8 Gm. (Dare); the white blood cell count showed 16,900 leukocytes with 58 per cent polymorphonuclears, 16 per cent metamyelocytes II, 8 per cent metamyelocytes I, 14 per cent lymphocytes, 2 per cent eosinophils and 2 per cent monocytes. The Wassermann reaction of the blood was negative.

Despite progressive asthenia, the patient felt comfortable during the first four weeks of her stay in the hospital. She became slovenly in her habits and lost all modesty. No changes in voice were noted. The weight gradually fell from 156 to 150 pounds (70.8 to 68 Kg.), and edema of the feet and legs disappeared. The temperature fluctuated between 98 and 101 F. Readings of the blood pressure taken frequently varied from 180 to 168 mm. of mercury systolic and from 138 to 125 diastolic.

Roentgenologic studies were reported as showing several small and large circumscribed areas of increased density in both pulmonary fields suggesting the presence of metastatic neoplasm. The bones of the skull showed no changes; the sella turcica was normal, measuring 10 mm. in anteroposterior diameter and 6 mm. in depth, and the clinoids were well formed and preserved. A slight degree of rarefaction was noted in the thoracic and lumbar portions of the spine. Roentgenograms of the long bones and of the heart showed no abnormalities.

On January 4 the Aschheim-Zondek test was negative.

On January 9 the basal metabolic rate was + 3 per cent.

Several urinalyses revealed proteinuria, the protein content varying from 1 to 4 plus; the specific gravity varied from 1.012 to 1.015; occasionally there were 1 or 2 white blood cells and as many red blood cells per high power field. No reducing or acetone bodies were detected. The results of determinations of urobilinogen were as follows: on January 9 a positive reaction was obtained with a 1:80 dilution; on January 10, with a 1:320 dilution; on January 16, with a 1:80 dilution, and on January 26, with a 1:80 dilution.

The dextrose tolerance test, on January 20, gave the following results: during fasting, 81.3 mg.; thirty minutes after ingestion of 100 Gm. of dextrose, 121.2 mg.; at the end of sixty minutes, 166.7 mg.; at the end of one hundred and twenty minutes, 173.9 mg., and at the end of one hundred and eighty minutes, 162.6 mg., per hundred cubic centimeters of blood.

Chemical studies of the blood made on January 22 showed: nonprotein nitrogen, 30 mg. per hundred cubic centimeters; sugar, 84 mg., and serum calcium, 11.4 mg. The icteric index was 15; the van den Bergh test gave a direct immediate positive and an indirect positive (qualitative) reaction.

During the last two weeks of the patient's life, Dr. Robert T. Frank of the Mount Sinai Hospital made hormonal studies on her blood and urine and reported the following results: "The urine contained as much as 5,000 mouse units of estrogenic substance per liter, a quantity far exceeding that found in pregnancy. As a control, however, the Friedman test was performed on two rabbits with the same urine, but a negative reaction was obtained. There was no excess of the

gonadotropic factor in the urine. The venous blood contained 1 mouse unit to 40 cc., which is a normal value. In other words, as far as the humoral condition was concerned, the findings were essentially normal except for the tremendous over-excretion of estrogenic substance in the urine." No analysis was made for androgenic substance.

Because new purpuric areas were repeatedly noted in the skin and a Rumpel-Leeds test (with pressure of 150 mm. of mercury) resulted in the appearance of myriads of purpuric spots over the dorsal aspect of the wrist, Dr. Connery of the hematologic service was asked to see the patient. On January 22, nine days before the patient's death, he reported the following results of tests on the blood: red blood cells, 3,310,000; hemoglobin (Klett and Newcomer), 54 per cent (9.7 Gm.); color index, 0.82; mean corpuscular hemoglobin, 27 micromicrograms (the normal amount is from 27 to 32 micromicrograms); mean corpuscular volume, 104 cu. mm. (the normal amount is from 80 to 94 cu. mm.); platelets, 157,000 per cu. mm.; bleeding time (Duke) six and a half minutes; coagulation time (Lee and White), eight and a half minutes, nine minutes, twelve minutes, ten minutes and ten and a half minutes, respectively, in five tests; fragility of the red blood cells (Sanford), from 0.48 to 0.32 per cent (control, from 0.44 to 0.32 per cent); erythrocyte sedimentation rate (Plass and Rourke), 87.5 per cent of total possible settling in one hour (upper limit of normal, 65 per cent); serum bilirubin, 1.7 mg. per hundred cubic centimeters.

The results of the differential count were reported by Dr. Connery as follows: 62 per cent polymorphonuclears, 20 per cent metamyelocytes II, 5 per cent metamyelocytes I, 1 per cent myelocytes and 10 per cent lymphocytes. The smear also showed 3 normoblasts per hundred white blood cells and moderate qualitative regenerative changes in the red blood cells. There were 6.6 per cent reticulocytes.

Dr. Connery expressed the opinion that the patient presented the following evidence of a hemolytic factor: (1) anemia with striking qualitative regenerative changes; (2) the presence of fragmented red cells and of many nucleated red cells; (3) an increased percentage of reticulocytes; (4) leukocytosis with a striking shift to the left; (5) an increased amount of urobilinogen in the urine, and (6) pertinently increased fragility of the red cells.

On January 25, the patient's temperature rose to 103.4 F. and a large abscess was noted on the upper portion of the left thigh, from which hemolytic streptococci were recovered in pure culture. Later that day she became comatose, and a lumbar puncture was made. The spinal fluid escaped under normal pressure; it was clear and colorless and contained a normal amount of reducing bodies, no globulin and 14 lymphocytes per cubic millimeter.

The patient went rapidly downhill. She became incontinent of urine and feces; the striae over the lower portion of the abdomen began to suppurate; her temperature remained at 103 F. and she died on January 31.

Autopsy.—Autopsy was performed two hours after death.

Macroscopic Examination: The results of external examination conformed to the aforementioned observations. Many of the striae were found to be ulcerated, some showing raised bullae filled with serous or purulent fluid. On the inner aspect of the left gluteal fold and extending forward to the region of the perineum was an area of diffuse inflammatory edema about 10 by 12 cm., perforated by many irregular ulcerations of varying size. On section the increase in depot fat was noted everywhere.

On dissection of the abdominal viscera, the right kidney was found displaced downward by a large tumor situated at its upper pole (fig. 2). Posteriorly the

tumor completely compressed the inferior vena cava and was firmly attached to the right lobe of the liver. It measured 15 by 18 by 16 cm. exclusive of the hepatic portion. The tumor was lobulated and encapsulated for the most part. The right kidney was intact and normal except for its displacement. In the tumor no trace of the right adrenal could be found.

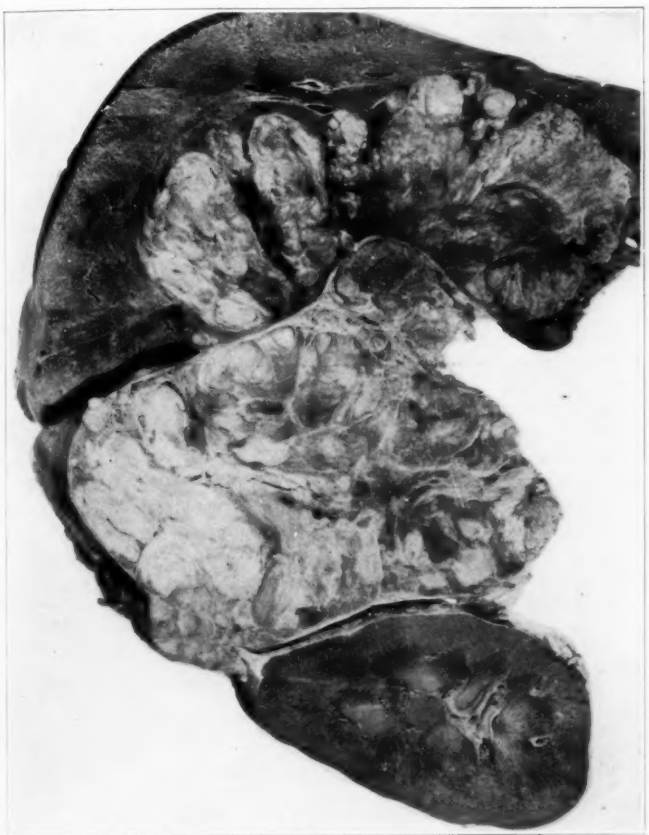

Fig. 2.—Photograph of the adrenal tumor, showing its relation to the liver and kidney.

Cut section of the tumor [11] showed an irregular lobulated appearance. Some areas were butter-yellow; others were necrotic, and others were the seat of recent

11. Several pieces of tumor were extracted for a pressor substance by Dr. Goettler, of the chemistry laboratory of the Bellevue Hospital, after the method

(Footnote continued on next page)

and old hemorrhage. The apparently best preserved portions of the tumor had a distinctly grayish-pink hue and were fleshy and fairly firm. Section of the liver and tumor in the frontal plane showed deep invasion of the right lobe, with pressure atrophy of the adjacent parenchyma and a few scattered metastases beyond. Thrombi were occasionally found in the hepatic veins and were readily extruded. The intact parenchyma of the liver showed the markings of chronic passive congestion. The structures of the hilus and gallbladder were normal. Dissection of the inferior vena cava from its opening in the right auricle showed it to be filled with soft tumor deposits.

There was no evidence of thymic tissue in the precordial and superior mediastinal fat.

The lungs contained numerous metastatic nodules in otherwise intact parenchyma.

The heart was not enlarged. The left ventricle was contracted; its walls were of normal thickness. The endocardial structures were intact. The aorta was elastic and of narrow caliber. Its intima was smooth and free from visible atheroma.

The left adrenal was small and wrinkled. On section the cortex seemed narrow and the medulla poorly defined; there was no autolysis.

The ovaries were small and firm and cut with increased resistance. No cysts or traces of lutein tissue were seen.

The bones of the skull, ribs and sternum were normal.

The pancreas, thyroid and parathyroids showed no changes.

All the other organs showed no macroscopic changes.

Pituitary Body: This was removed with the encasing sella turcica. After it was dissected no macroscopic changes were seen. The gland was not enlarged. It measured 13 mm. in anteroposterior diameter, 14 mm. in the lateral dimension and 6 mm. vertically. A sagittal section was cut through the gland, including the stalk. No abnormality was seen on either cut surface.

Microscopic Examination: Sections of the tumor (fig. 3) revealed a new growth consistent with the picture of carcinoma arising in the cortex of the adrenal. The metastases showed the most consistent morphology and the best preserved cells. Degenerative changes were numerous in all the portions studied. Tissue fixed in absolute alcohol and stained by Best's method showed no glycogen in the sections taken.

The examination of the vascular tree revealed no significant changes indicative of preexisting hypertension except focal arteriolosclerosis in the kidney and some focal thickening of the basement membrane in an occasional glomerulus. The tubules showed widespread degenerative changes; many of them contained red cell casts.

There was evidence of hematopoiesis in the spleen. There was also slight increase in reticulum strands in the lymphoid follicles.

Section of the thyroid showed it to be in a resting state approaching hypoplasia.

Twenty-eight sections of each ovary (fig. 4) at depths of 50 microns were prepared. One oocyte was seen in each series, one fairly well preserved and one

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given by Hick (A Suprarenalin-Producing Pheochromocytoma of the Suprarenal Gland, Arch. Path. **15**:665 [May] 1933). Professor Wallace, of the department of pharmacology, who used the same material in testing a dog, found no elevation of blood pressure. Dr. Robert T. Frank, of the Mount Sinai Hospital, found each gram of the tumor tissue to contain twice the amount of estrogenic substance that could be recovered from a gram of the normal spleen from the same patient used as control.

Fig. 3.—Photomicrograph of a section through one of the tumor nodules, showing the compact arrangement of the cells, chiefly in cords. Marked variation in size and shape and staining affinity can also be seen.

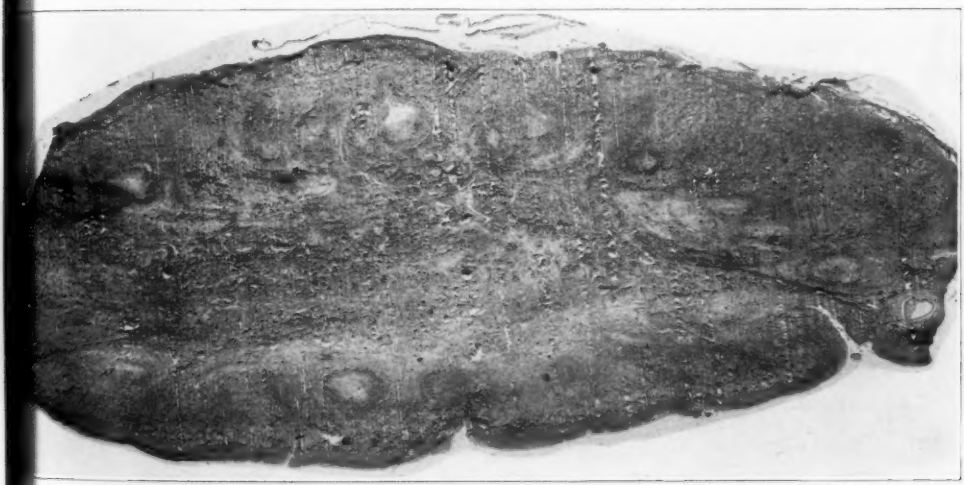

Fig. 4.—Photomicrograph (low power magnification) of a section of the right ovary made in the longest dimension. One maturating follicle can be seen in the lower right corner. Elsewhere the ovary shows marked fibrosis with atresia of the follicles.

undergoing degeneration. Both ovaries were relatively bloodless and showed an unusual amount of progressive atresia of the follicles in all stages. In some fields scarcely any primordial follicles were seen, and in others as many as eight were present; these too were in various stages of atresia. There were a few surface tags of adhesions and inclusion of peritoneum.

Sections of the endometrium showed atrophy of the glands, marked edema and swelling of the outer two thirds of the mucosa.

Sections of all parts of the pancreas showed well preserved acinar tissue. The islands of Langerhans seemed normal except for focal hemorrhage in an occasional islet.

The left adrenal was cut into five blocks, and many sections from each block showed no chromaffinic granules. The medulla appeared scanty and was barely distinguishable from the cortex; the cortex was narrow and the zona reticularis atrophic. The central vein and its branches showed irregular hypertrophy of its muscular wall.

The pineal body exhibited no noteworthy changes.

The sections of the other organs with the exception of the pituitary gland revealed no significant alterations.

Pituitary Gland: Sagittally cut serial sections (5 microns thick) were prepared of the halves of the gland after the tissue had been fixed in Zenker's fluid and embedded in paraffin. About thirty-five sections were lost in preparation.

In one block a miliary oval circumscribed nodule (fig. 5) was found in the inferior portion of the anterior lobe just within the capsule. It measured 1 mm. by 850 microns and appeared to have compressed the surrounding tissue.

The first impression on seeing sections stained with Delafield's hematoxylin, a dilute Giemsa solution or iron hematoxylin and eosin was that the nodule represented a basophil adenoma.

However, when special cytoplasmic stains[12] were employed, and particularly after sections had been mordanted in 3 per cent potassium di-chromate for several days, it became clear that most of the cells in the nodule contained no chromophilic granules.

The vast majority of cells (fig. 6) showed scanty ill defined cytoplasm without granules and were loosely arranged around dilated capillaries and in discrete clumps presenting no definite pattern. There were a few eosinophilic cells and recognizable basophils at the periphery and rarely in the central portion of the tumor.

While the majority of cells tended to take a feeble bluish-purple hue with hematoxylin, ordinary immersion in a 1 per cent aqueous solution of eosin gave them a reddish tint. The nuclei of many of the ill defined cells showed striking vesicular degenerative changes, and this feature was common to the basophils outside of the nodule. This was considered to constitute possible evidence of kinship. At times the nuclei were pyknotic and fuchsinophilic. These observations will be detailed later.

The capsule of the nodule (fig. 6) appeared to be composed of preexisting reticular and collagenous fibers (perhaps brought together by pressure atrophy of

12. The following technics and stains were used: Severinghaus' method; Bailey's method which employs acid violet and Altmann's aniline fuchsin; Mallory's aniline blue; the Weigert method employing gentian violet, iron hematoxylin; Heidenhain's azocarmine; Giemsa stains, and a new method introduced by Soós and Csizek (Die elektive Färbung der basophilen Granulen des Hirnanhanges, Endokrinologie **10**:410, 1932).

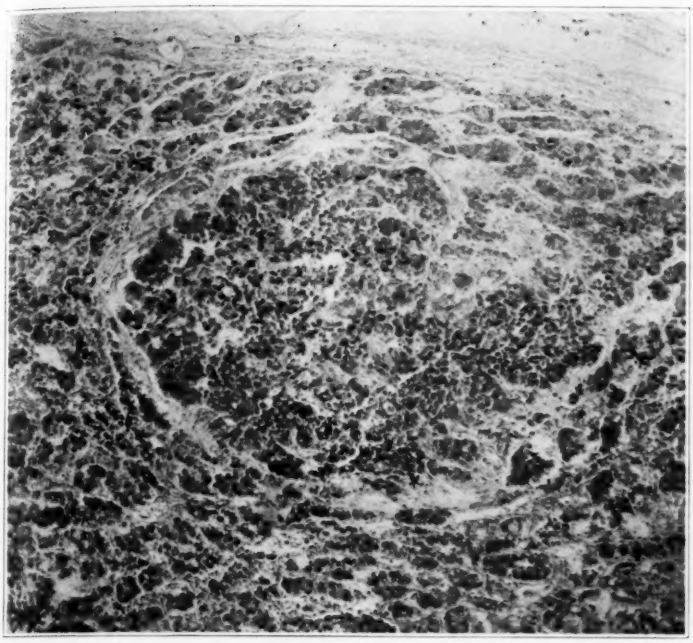

Fig. 5.—Photomicrograph (low power magnification) of a section through the adenomatous nodule in the anterior lobe of the hypophysis. Note the compression of the surrounding tissue, the poorly defined capsule and the irregular arrangement of the cells within the nodule.

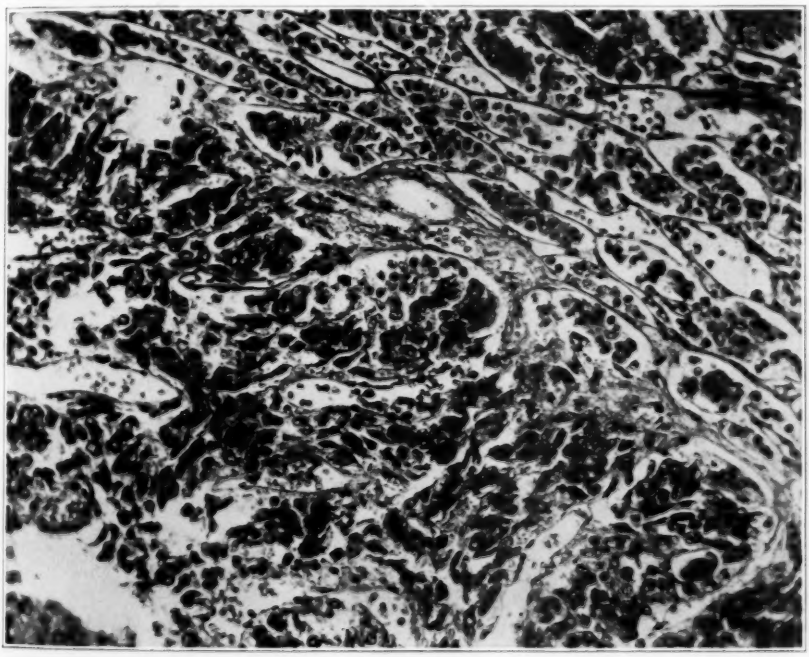

Fig. 6.—Photomicrograph of a section through the edge of the nodule shown in figure 5 (stained by the method of Foot and Foot for reticulum). Note the absence of reticulum fibers within the nodule; contrast the disorderly arrangement of the cells within the nodule with that in the adjacent intact pars anterior.

the intervening parenchyma). Externally the fibers were continuous with the stroma of the adjacent tissue. Little or no stroma was demonstrable in the tumor; this formed a sharp contrast to the remainder of the pars anterior.

Outside the nodule (fig. 7) the eosinophils were uniform in size, and their granules were brilliantly clear and easily demonstrated. A few degenerated ones were seen within the adenomatous nodule. Some transitional forms were encountered in all fields. The chief cells were not noticeably altered.

The basophils were conspicuously altered (fig. 7). While the size and affinity of the cytoplasm for the appropriate dyes indicated that they were beta cells, their granules were not demonstrated as such.[13]

Reference has been made to nuclear changes in many of the cells of the adenomatous nodule. Similar alterations were exhibited by the beta cells throughout the anterior lobe. Their nuclei wherever studied were enlarged. In some the swelling had increased their nuclear outline until it reached to just within the periphery of the cytoplasm. In others several clear vesicles were seen in a single nucleus, outlined by fine chromatinic lines, filling and giving the nucleus a lobulated appearance.

Elsewhere the nuclear membrane appeared to be dissolving and merging imperceptibly with the cytoplasm. In other cells small vesicles[14] (vacuoles) could be seen in what appeared to be a process of extrusion through the nuclear membrane. Amitotic division was encountered also, and multinucleated forms (of basophils) were found inside and outside of the nodule. Not infrequenly a pyknotic nucleus was seen, and in sections stained by the method of Severinghaus they were fuchsinophilic.

So-called *entgranulierten* (degranulated) cells were occasionally found both within and without the nodule. They were approximately the same size as the basophils elsewhere.

Sections of the hypothalamic region[15] and of other portions of the brain showed no pathologic changes.

Final Pathologic Diagnosis.—The final diagnosis was: carcinoma of the right adrenal gland with metastases to the liver, inferior vena cava and lungs; indeterminate adenoma of the pars anterior of the pituitary gland; selective vesicular degeneration of the beta cells of the hypophysis; atrophy of the ovaries and endometrium; slight atrophy of the left adrenal gland; slight hypoplasia of the thyroid gland; hypertrichosis; obesity; sepsis from striae infected with Streptococcus haemolyticus.

COMMENT

This case presents once more the opportunity to point out, as others before us have done, the important clinical observation that the syndrome here described is not specific for any single endocrine disturbance. The recent literature contains ample evidence that the same clinical picture may be associated with a basophil adenoma of the pituitary, hyperplasia or a tumor of the adrenal cortex, a tumor of the thymus or an arrhenoblastoma of the ovary.

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13. Three hundred cells counted showed no cytoplasmic granules. This is interesting since Bailey and Davidoff have found that in material fixed in Zenker's fluid the sublimate may produce artificial granulation simulating beta granules.

14. The vesicles exhibited no chromatism with any of the stains employed.

15. Dr. Lewis Stevenson examined the brain and reported the results of his examination.

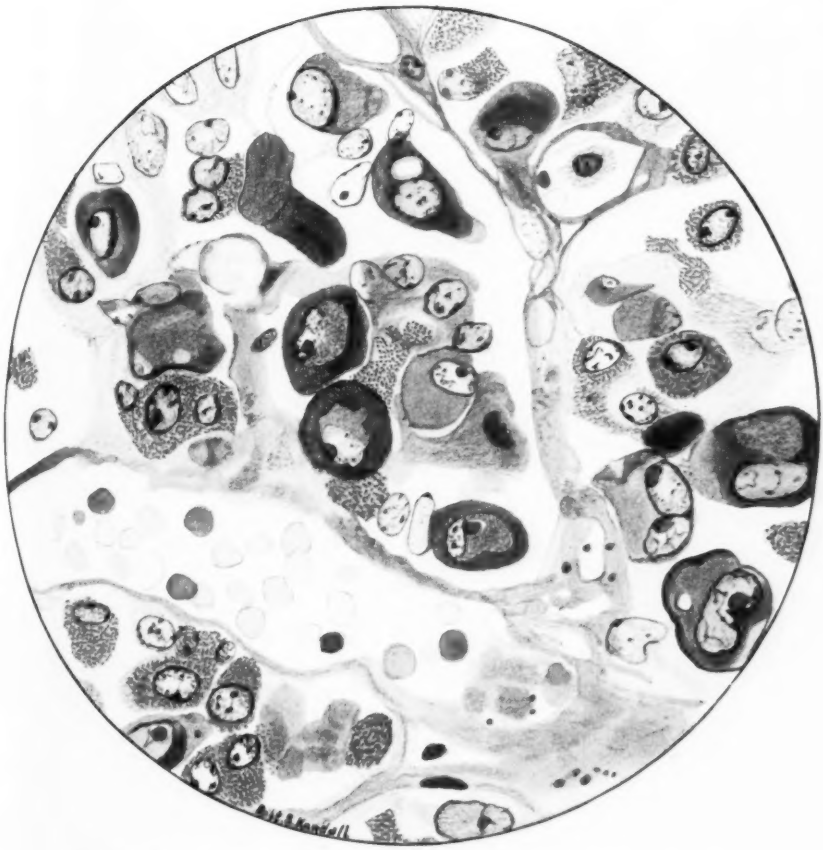

Fig. 7.—Camera lucida drawing (Leitz oil immersion lens 1/12, ocular 10×) of a field of a section of the pituitary gland, illustrating the loss of cytoplasmic granules in the beta cells, the marked vesicular swelling of the nuclei and the presence of large hyaloplasmic vesicles. Some basophils exhibit pyknotic nuclei which are fuchsinophilic. The section was stained by the Severinghaus modification of Masson's trichrome stain.

The relationship of the adrenal neoplasm to the clinical manifestations seems clear. The observations on the pituitary gland raise several questions, which we shall attempt to answer.

The nature of the tumor nodule in the pars anterior is difficult to determine. It partially satisfies the criteria given by Kraus [16] in his study of adenoma of the anterior lobe of the pituitary. It possesses a capsule and compresses the adjacent tissue. However, it is not composed of cells of one type. At its periphery are found various intact cells normal to the anterior lobe. The absence of reticular stroma within the nodule and the ill defined cell clumps which compose it indicate a focus of cells growing autonomously.

Unfortunately, these cells exhibit degenerative changes which mask their true nature. It seems best in view of inconclusive identification to call the nodule an indeterminate adenoma.

To determine whether or not the adenoma is merely coincidental, one should know the incidence of such tumors in the general population free from endocrine changes. Such data are not as yet available on a statistical basis. In a recent bulletin of the Mayo Clinic, Costello [17] is said to have studied 1,000 pituitary glands obtained at random in postmortem examinations of patients with no history of endocrine abnormality. Each hypophysis was sectioned serially at intervals of 1 mm. Approximately 20 per cent contained adenomas, and one fifth of these were basophil. The age and sex distribution and relation to pregnancy, however, are not given, and evaluation of Costello's figures must await full report.

The recent report of Close [18] is pertinent in this regard. He studied the incidence of pituitary adenomas in about 200 patients examined at necropsy and found such tumors in about 10 per cent of the glands, although they were not all serially sectioned. Without indicating the incidence according to age he noted that most of the adenomas occurred in persons over 45 who had a benign or malignant neoplasm elsewhere. He then studied 125 of these pituitaries in serial sections, 75 from patients with a true neoplasm elsewhere in the body, and 50 from persons over 45 in whom in a routine autopsy no other tumor was found. The incidence of adenoma of the pituitary gland is given by him as

16. Kraus, E. J.: Die Beziehungen der Zellen des Vorderlappens des menschlichen Hypophyse zueinander unter normalen Verhältnissen und in Tumoren, Beitr. z. path. Anat. u. z. allg. Path. **58**:159, 1914.

17. Costello, R. T., cited by Kepler, E. J.; Kennedy, R. L. J.; Davis, A. C.; Walters, W., and Wilder, R. M.: Suprarenocortical Syndrome and Pituitary Basophilism: Presentation of Three New Cases, Proc. Staff Meet., Mayo Clin. **9**: 169, 1934.

18. Close, H. G.: Lancet **1**:732 (April 7) 1934.

follows: (1) 10 per cent in all cases, (2) 44 per cent in cases of carcinoma, (3) over 50 per cent in cases of certain types of carcinoma (pancreatic, rectal and bronchial) and in cases of adenoma of the prostate. Thirty-seven, or approximately 95 per cent, of the adenomas were of chromophobe and none of the basophil type. Close's studies have led him to suggest a hormonal basis for the development of some pituitary adenomas in patients with carcinoma. It will be interesting if other cases of adrenocortical carcinoma associated with pituitary adenoma can be explained on the same basis. As Close pointed out, the development of multiple tumors may be merely a part of the constitutional tendency to tumor formation.

To obtain some idea of the age relationship of pituitary adenomas in persons free from endocrine disturbances, we have analyzed the data published by Erdheim and Stumme[19] and Kraus,[16] who studied their material in serial histologic sections. The former found adenomas or foci of adenomatoid hyperplasia in 12 of 119 patients. Kraus found adenomas in 25 of 300 pituitaries. There is an incidence in this series comparable to that reported by Erdheim. An analysis of the age incidence in the combined reports (we have deducted 3 cases because of associated endocrine disorders) reveals the following distribution:

From 1 to 10 years	1 case
From 11 to 20 years	1 case
From 21 to 30 years	4 cases
From 31 to 40 years	4 cases
From 41 to 50 years	10 cases
From 51 to 60 years	7 cases
From 61 to 70 years	1 case
From 71 to 80 years	2 cases
From 81 to 90 years	2 cases
Age unknown	2 cases
Total	34 cases

It is interesting that in 25, or 73 per cent, of these 34 cases the patient was between the third and the seventh decade. The inference is plain then that the nodules[20] in the case here reported may not be dismissed as being merely coincidental.

No light can be thrown on the nature of the nuclear changes described for the cells of the pituitary adenoma and the beta cells

19. Erdheim, J., and Stumme, E.: Ueber die Schwangerschaftsveränderung der Hypophyse, Beitr. z. path. Anat. u. z. allg. Path. **46**:1, 1909.

20. We are aware of the impossibility of assigning a physiologic or pathophysiologic rôle to the nodules, especially since the literature contains reports (some cited here) of cases of similar tumors without endocrine disturbance.

outside. Inability to demonstrate the granules of these cells alone is of little significance because of possible postmortem change. However, this observation and the severe nuclear regressive changes together seem to indicate a selective pathologic process.[21] The integrity of the chief cells and the eosinophils serves to emphasize the selectivity of the process.

Hypophyses[22] from patients dying of other types of malignant metastasizing newgrowths, sepsis or trauma and the hypophysis of another patient with an adrenal tumor have been examined by us and have failed to show similar cellular changes. The pituitary-adrenal relationship may be invoked as possibly encompassing these selective changes in some peculiar and inconsistent manner. Proof awaits additional cases of similar involvement and particular search of the hypophysis for similar lesions.

Are the changes in the pituitary gland evidence of a reciprocal adrenal-pituitary relationship? To consider that they may be seems reasonable, yet little evidence is available to establish this point.

Numerous observations show the influence of the pituitary gland on the adrenal cortex, but surprisingly few well controlled studies bear on a converse influence. Smith[23] showed that the adrenal glands of hypophysectomized rats shrink rapidly (in six days) to one-half the size of the adrenal glands of controls and that this shrinkage is almost entirely due to retrogression of the cortex. He showed further that atrophy of the adrenal cortex does not occur when only the posterior lobe of the pituitary is ablated and, lastly, that the atrophic glands of the hypophysectomized rats can be promptly restored to normal or near normal by daily homeotransplants of anterior lobe of the pituitary.

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21. Since this report was submitted A. C. Crooke (J. Path. & Bact. **41**:339, 1935) has reported the occurrence of selective hyaline changes with loss of granules in the cytoplasm of the basophil cells of the pituitary gland in 12 examples of the clinical syndrome exhibited by our patient. His cases include patients with basophil adenoma of the pituitary gland, neoplasm of the thymus and neoplasm or hyperplasia of the adrenal cortex. In a later personal communication and after examining a section of the pituitary gland of our patient Dr. Crooke concluded that our patient exhibited the same cytoplasmic change in a final stage. (These changes are illustrated in figure 8 of the aforementioned article by Crooke.) He added (Feb. 7, 1936) that he had found this hyaline change in 29 cases of so-called basophilism associated with adenoma in the pituitary gland, neoplasm of the adrenal cortex or carcinoma of the thymus.

22. Somewhat similar changes have been claimed by Kraus[27] to occur in the basophils in the hypophyses of patients dying of Addison's disease—a clinical syndrome and adrenal disorder unrelated to the one under discussion.

23. Smith, P. E.: Hypophysectomy and Replacement Therapy in Rat, Am. J. Anat. **45**:205, 1930.

Putnam, Teel and Benedict [24] recently reported cortical adenomatosis of the adrenal gland in 1 of 2 dogs rendered acromegalic by the intraperitoneal injection of anterior pituitary extract. Thompson and Troppoli,[25] working in Cushing's laboratory, were believed by him to have demonstrated experimentally in rats that pituitary gonadotropic extract serves as a stimulant of the adrenal cortex. Collip, Anderson and Thomson [26] claimed to have isolated chemically from the anterior lobe of the pituitary an "adrenotropic factor" which when administered to 125 hypophysectomized rats caused an increase of from 50 to 300 per cent in the weight of their adrenals.

Supplementing these experimental reports are a number of clinical observations which demonstrate the interrelationship. It is well known, for example, that in anencephalic fetuses in which the anterior portion of the brain is involved the adrenal cortex is aplastic or absent. Mention has been made of the cases of "pituitary basophilism" described by Cushing,[7] in the majority of which there was definite hyperplasia of adrenal cortex.

The foregoing citations illustrate the influence of the pituitary gland on the adrenals. The direct effect of the adrenals on the pituitary has not as yet been definitely determined. Clinical sources for such a study have been limited practically to cases of Addison's disease. Kraus,[27] Kiyono [28] and Berblinger [29] have described quantitative and qualitative changes in the basophilic cells of the pituitary in such cases. These cells diminish in number and show regressive changes in their nuclei and cytoplasm. The chief cells increase at the expense of the basophils. As to the eosinophils, there is no agreement in the results of observations.

The experimental studies on the adrenal-pituitary relationship have recently been reviewed by Houssay,[30] who found no unanimity of opinion among the various investigators and concluded that "it has not yet been demonstrated that the suprarenal influences the hypophysis, although this is probable." He pointed out that the short survival

24. Putnam, T. J.; Benedict, E. B., and Teel, H. M.: Studies in Acromegaly: VIII. Experimental Canine Acromegaly Produced by Injection of Anterior Lobe Pituitary Extract, Arch. Surg. **18**:1708 (April, pt. 1) 1929.

25. Thompson and Troppoli, cited by Cushing.[7]

26. Collip, J. B.; Anderson, E. M., and Thomson, D. L.: The Adrenotropic Hormone of the Anterior Pituitary Lobe, Lancet **2**:347, 1933.

27. Kraus, E. J.: Zur Pathologie der basophilen Zellen der Hypophyse, Virchows Arch. f. path. Anat. **247**:421, 1923.

28. Kiyono, H.: Die Histopathologie der Hypophyse, Virchows Arch. f. path. Anat. **259**:388, 1926.

29. Berblinger, W.: Die Störungen der inneren Sekretion der Keimdrüsen und die Sexualhormone, Klin. Wchnschr. **7**:1673 (Sept. 2); 1721 (Sept. 9) 1928.

30. Houssay, B. A.: Relaciones entre la hipófisis y las suprarrenales, Prensa méd. argent. **20**:1563, 1933.

of the adrenalectomized animals and the severe malnutrition which may of itself cause changes in the pituitary are two serious obstacles that have been encountered in this work.

Martin [31] has studied the effect of the adrenals on the pituitary. When complete adrenalectomy was performed on adult female and on normal and castrate male rats, it produced a marked decrease in the gonad-stimulating hormone of the anterior lobe. Changes in the cytologic picture of the hypophyses of these rats were also noted. A brief statement refers to a decrease in the size and staining reaction of the oxyphils (alpha cells) of the pars anterior. The effect on the basophils was not constant. A more detailed report is still to be made.

While we reviewed the literature on the subject, it occurred to us that the reports of cases of adrenal neoplasm similar to our own might include studies of the pituitary gland or give evidence of the disturbances which might be considered manifestations of pituitary disorders.[32] The following reports were found which tend to show that manifestations of pituitary disturbance may occur in the presence of an adrenal tumor: Oppenheimer and Fishberg [33] reported the case of a 24 year old man who had hypertension due to a tumor of the adrenal cortex and who had an acromegalic appearance. It cannot be gathered from this report whether or not the appearance antedated the other clinical signs.

Long and Gray [34] reported a case of metastasizing carcinoma of the adrenal cortex in a man aged 45 in whom an acromegalic appearance developed while he was under observation during the last six months of life. At autopsy casual sections of the pituitary were examined and were reported to show an "overgrowth" of eosinophilic and chromphobic cells with marked predominance of the former.

Mathias [10] described an 18 year old girl who had hypertrichosis with a well marked beard from the age of 3 years and at the age of 18 died of a metastasizing neoplasm of the adrenal cortex. Serial sections of the pituitary gland showed a marked "increase" [35] of the eosinophilic

31. Martin, S. J.: The Effect of Complete Suprarenalectomy on the Oestrual Cycle of the White Rat with Reference to Suprarenal-Pituitary Relationship, Am. J. Physiol. **100**:180, 1932.

32. Moehlig (Pituitary Gland and Suprarenal Cortex, Arch. Int. Med. **44**:339 [Sept.] 1929) has made the statement ". . . that acromegaly is associated at times with tumor of the adrenal cortex" (p. 342), but he cites no references or cases.

33. Oppenheimer, B. S., and Fishberg, A. M.: The Association of Hypertension with Suprarenal Tumors, Arch. Int. Med. **34**:631 (Nov.) 1924.

34. Long, H. W., and Gray, J. W.: Acromegaly Associated with Adrenal Tumor, M. J. & Rec. **119**:38, 1924.

35. Rasmussen (Am. J. Path. **5**:263, 1929) has shown that estimates of increases are not reliable and that quantitative determination of the relative numbers of each type of cell is necessary in order to determine changes in number.

cells and an overgrowth of the chief cells, which in one place had the characteristic of the cells of an adenoma.

In view of these reports the changes in the pituitary described in our case assume more significance. Elucidation awaits further evidence based on cases in man, like that of Crooke, as well as experimental proof to show that disturbances of the adrenal cortex may affect the pituitary gland functionally or structurally.

Finally, there is an interesting hormonal aspect to this case. As will be recalled, there was an enormous increase in the amount of estrogenic substance in the patient's urine, a normal amount in the blood and a negative Friedman test for pregnancy. Exactly the same observations were recorded in a case recently observed by Frank.[36] His patient was a 33 year old woman who presented essentially the same clinical syndrome as our patient and at necropsy was found to have a tumor of the adrenal cortex and no adenoma of the pituitary. These 2 cases led Frank to believe that in the future such hormonal findings may prove diagnostic of tumor of the adrenal cortex in contradistinction to adenoma of the pituitary, but he awaited further opportunities to confirm this suspicion.

Since our patient showed an unusual amount of atresia of the ovarian follicles and atrophy of the endometrial glands, we were at a loss to account for the source of the huge amount of estrogenic substance found in her urine. It therefore was of interest to us to learn that recently Migliavacca[37] showed experimentally in guinea-pigs, whose hypophyses had been irradiated to eliminate their hormonal influence, that a commercial preparation of adrenal cortex causes an intense luteinization of the ovarian follicles even in the presence of obliterating or cystic atresia of the follicles. Since Dr. Frank found somewhat larger amounts of estrogenic substance in the tumor material from our patients than in the material from an indifferent organ (spleen), it may be that the neoplasm was the source of the hormone.

SUMMARY

The case is reported of a 19 year old girl who presented hirsutism, hypertension, obesity and striae atrophicae in life and at necropsy was observed to have a metastasizing carcinoma of the adrenal cortex and an indeterminate miliary adenoma of the anterior lobe of the pituitary gland.

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36. Frank, R. T.: Suggested Test for Functional Cortical Adrenal Tumor, Proc. Soc. Exper. Biol. & Med. **31**:1204, 1934.

37. Migliavacca, A.: Irradiazione röntgen dell'ipofisi e riattivazione parziale dell'ovaio sotto l'azione dell'ormone corticosurrenale, Ztschr. f. Zellforsch. u. mikr. Anat. **17**:662, 1933.

Selective degenerative changes were noted in the nuclei of the beta cells of the pars anterior of the hypophysis.

Although data are not conclusive, evidence is given which tends to show that the pituitary adenoma is not merely a coincidental finding.

Attention is drawn to the co-existence of clinical manifestations or pathologic evidence of changes in the pituitary gland in similar cases of metastasizing adrenal neoplasm recorded in the literature; this and other evidence of the effect of adrenal disturbances on the pituitary gland are discussed.

Marked overexcretion of estrogenic substance in the urine was noted during life, and this is discussed in relation to the atresia and atrophy of the ovaries and endometrium.

CONTROL OF HYPERTHYROIDISM FOLLOWING PARTIAL THYROIDECTOMY

BY REMOVAL OF UNUSUALLY SMALL AMOUNTS OF THYROID TISSUE

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The results of surgical treatment of exophthalmic goiter are today most gratifying and compare favorably with those of other operations of equal magnitude. As practiced at the Mayo Clinic, the operation of subtotal thyroidectomy, in which is preserved a posteromesial portion of each lobe equivalent to from a sixth to a third of a lobe of normal size, is comparatively free from technical complications, such as parathyroid tetany and injury to the inferior laryngeal nerve. Since the standardization of the preoperative treatment with iodine, the operation has been performed on approximately nine thousand patients with exophthalmic goiter, with a mortality of 0.8 per cent. The late results are equally gratifying. Within from two to four weeks after operation the basal metabolic rate is usually within normal limits, and after the lapse of one, three and five years more than 90 per cent of the patients consider themselves improved or as well as they were before the onset of the disease and present evidence to indicate that they are free from hyperthyroidism. It is estimated that the death rate for patients who have successfully undergone thyroidectomy is no greater than that for an average group of persons.

It is also estimated that after the lapse of five years from 2 to 5 per cent of the patients have sufficient evidence of recurrence of symptoms to warrant a secondary operation. In nearly all cases of recurrent exophthalmic goiter regeneration of the remaining portion of the thyroid gland takes place, so that the examiner usually is able to palpate some thyroid tissue, although it is common at operation to find far greater enlargement of the gland than was indicated on physical examination. The reason for the failure of the examiner to estimate the size of the gland more accurately is that the greater portion of the enlargement may be concealed as retrotracheal or substernal projections which are beyond the reach of his fingers. This tendency in cases of recurrent

From the Division of Medicine and the Division of Surgery, the Mayo Clinic.

goiter for the remaining portion of the thyroid gland to project behind the trachea and into the upper part of the mediastinum is readily explained by the presence of scar tissue, which commonly forms in front of the resected portion of the lobe. Since scar tissue is more unyielding than other soft structures of the neck, any subsequent growth of the thyroid gland will naturally project in the direction of least resistance, that is, retrotracheally or substernally. These facts are mentioned only to emphasize the point that in cases of suspected recurrent hyperthyroidism failure to palpate any appreciable amount of thyroid tissue does not necessarily exclude the presence of such tissue.

Several factors may be responsible for recurrence. Some of the probable factors are the amount of thyroid tissue left at operation, the recurrence or persistence and the intensity of the unknown force causing the disease and persistence in the postoperative use of iodine. Undoubtedly other factors also exist. Some patients with recurrent exophthalmic goiter may have the evidences of the disease brought permanently and completely under control by the use of compound solution of iodine alone, while in many cases further resection of the thyroid gland is necessary to bring the disease under complete control. All the factors which determine the controllability with iodine are not known, but in a study of a group of these cases it immediately becomes apparent that the amount of thyroid tissue present is an important factor. A large proportion of patients with recurrent exophthalmic goiter who have such a small remnant of thyroid gland that it cannot be palpated will easily lose all symptoms and signs of exophthalmic goiter after compound solution of iodine has been administered for two weeks or more. In a recent study of a series of cases of recurrent exophthalmic goiter it was found that in 25 per cent the symptoms were so controlled.[1] In most of these cases the disease will be kept under control for years at least by the continued administration of iodine. The majority of patients with a more easily palpable thyroid gland at the time of recurrence will not have the disease sufficiently controlled by iodine to warrant further avoidance of surgical treatment, and in these cases further resection of the thyroid gland has been resorted to in this clinic in order to complete the control of the disease. The latter procedure has been carried out also whenever control of hyperthyroidism has not been obtained within a few weeks by the administration of iodine.

The three cases reported here are of interest because of the maintenance of the amount of thyroid tissue present at the time of the recurrence of exophthalmic goiter and because of the reactions of the patients both before and after a second operation.

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1. Haines, S. F.: The Use of Iodine in Recurrent Exophthalmic Goiter, West. J. Surg. **42**:449 (Aug.) 1934.

REPORT OF CASES

CASE 1.—A married woman 31 years of age was first seen at the clinic in June 1925, when she was examined because of obesity. The basal metabolic rate at that time was +5 per cent, and the blood pressure in millimeters of mercury was 118 systolic and 88 diastolic. A restricted diet was outlined for the patient but was not followed, and the weight increased to 280 pounds (127 Kg.). In 1930 the dietary restriction was rigidly adhered to, and 112 pounds (50.6 Kg.) was lost in nine months. During that time the patient complained of dyspnea on exertion and of insomnia; there had been short attacks of palpitation for three months and some looseness of the stools for one month. On March 23, 1931, the patient was again examined. She was nervous and emotionally upset, the skin was warm and there was a slight fine tremor of the fingers. The thyroid gland was palpable

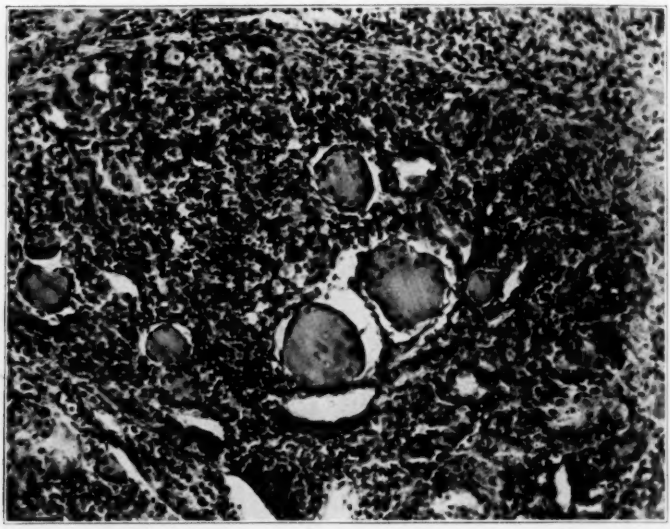

Fig. 1.—Hypertrophic parenchymatous thyroid tissue, showing moderate thyroiditis and slight fibrosis.

and firm. The basal metabolic rate on three consecutive days was +52, +43 and +44 per cent. The readings of the systolic and the diastolic blood pressure were 140 and 84, 134 and 70, and 130 and 78, respectively.

The patient was given 10 minims of compound solution of iodine three times daily, and the basal metabolic rate after six days was +30 per cent and after eleven days +27 per cent. There was marked improvement in the patient's nervous state and strength. On April 9 partial thyroidectomy was performed. The thyroid gland was small and hard, the lobes being very slightly larger than normal. The amount of tissue preserved was estimated to be about a fifth of a normal-sized lobe on the right and about a fourth of a normal-sized lobe on the left. Pathologic examination of the excised portions of thyroid gland revealed hypertrophic parenchymatous tissue, with evidence of moderate thyroiditis and fibrosis (fig. 1). The total weight of the tissue removed was 6 Gm. For six weeks after

the operation the patient's condition was improved. She had attacks of palpitation, but these were rare. She then noticed a loss of strength, increased nervousness and mental unrest. The attacks of palpitation increased in frequency and were associated with tachycardia, giddiness and weakness. There had been constant anorexia since thyroidectomy was performed and a loss of 5 pounds (2.3 Kg.).

The patient returned for examination on September 15. The blood pressure on two occasions was 130 systolic and 60 diastolic and 142 systolic and 72 diastolic; the pulse rate ranged from 102 to 104 beats per minute. The skin was warm, and there was marked weakness of the quadriceps muscles. The thyroid gland was not palpable. The basal metabolic rate on two occasions was +44 and +46 per cent. The patient was still taking compound solution of iodine. On September

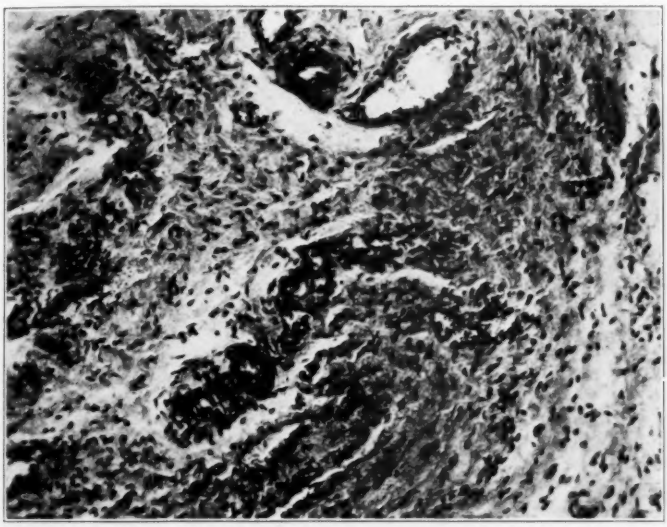

Fig. 2.—Scar tissue containing a very few thyroid acini.

18 and 19 treatment with roentgen rays was given over the thyroid gland, and the patient was allowed to return home, with instructions to continue the use of iodine.

On October 14 the patient returned to the clinic. There was such marked weakness of the thighs and legs that she had fallen frequently and was considerably bruised. Also, she had fainted a number of times. The basal metabolic rate was +40 and +44 per cent on two occasions, and readings of the systolic and the diastolic blood pressure were 136 and 76, and 140 and 78, respectively. Further resection of the thyroid gland was undertaken on October 23. The amount of thyroid tissue on each side was estimated at less than a tenth the size of a normal-sized lobe. No thyroid tissue could be revealed retrotracheally or substernally. A very small amount of tissue was removed from each side, one portion containing more parathyroid than thyroid tissue. The right inferior thyroid artery was ligated. Less than 1 Gm. of tissue was removed. Microscopically, the excised tissue consisted partly of parathyroid tissue and partly of scar tissue containing

very few thyroid acini (fig. 2). On October 28 the basal metabolic rate was +18; on October 30, +11, and on November 4 +1 per cent. The basal metabolic rate was determined daily and showed a constant gradual fall till November 11, when it reached —6 per cent.

At that time the patient was enthusiastic about the state of her health. However, on December 15 she returned, complaining of fatigue, of lack of energy and endurance and of excessive sleepiness, so that a nap of two or three hours was necessary in addition to thirteen hours of sleep at night. She was very intolerant to cold. She had noticed swelling of the face, neck and abdomen since the latter part of November. The weight had increased 19 pounds (8.6 Kg.) since the second operation. Her appearance was typical of myxedema; the skin was dry, scaling and cold, there was edema of the subcutaneous tissues, the recovery of the

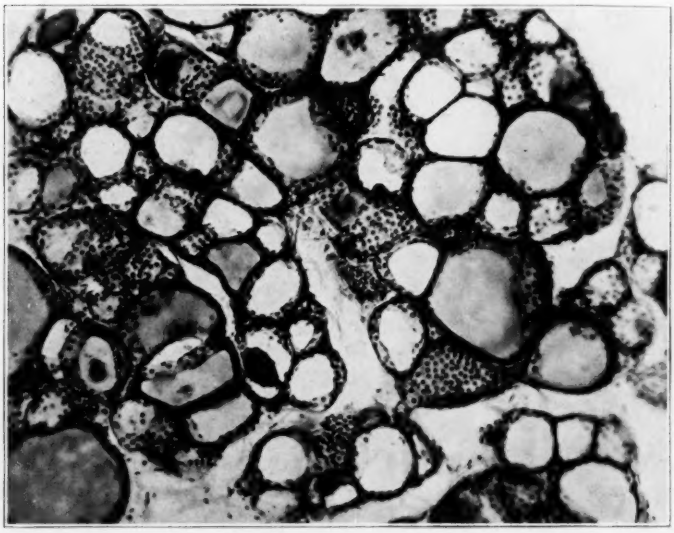

Fig. 3.—Colloid thyroid tissue.

tendon reflex was slowed and the voice was low, hoarse and slow. The basal metabolic rate was —16, —16 and —17 per cent on three occasions. The value for cholesterol was 407 mg. per hundred cubic centimeters of blood. One grain (0.065 Gm.) of thyroid was given daily, and the basal metabolic rate rose to —5 and —6 per cent. The cholesterol content was 222 mg. per hundred cubic centimeters of blood.

On Jan. 12, 1932, the patient was seen for the last time. The basal metabolic rate at that time was —9 per cent, and there were no evidences of organic disease. She was pregnant for the first time in twelve years of married life. She had a normal delivery of a normal child. In October 1932 she reported that she was still taking thyroid and was well.

Case 2.—A man aged 37 was examined on Aug. 12, 1930. Eight years before, in the course of a general examination, the basal metabolic rate was +8 per cent. Readings of the systolic and diastolic blood pressure at that time were 138 and

100, 124 and 82, and 118 and 80, respectively; the pulse rate varied from 72 to 116. At the time of examination at the clinic he had a history of nervousness, rapid heart beat, headache, insomnia and palpitation and tachycardia for five months. There was marked tremor of the hands. The patient was restless and stimulated. The thyroid gland was easily palpable, each lateral lobe measuring 2.5 by 5.5 cm. The blood pressure was 150 systolic and 90 diastolic and the pulse rate 120. The basal metabolic rate was +13 per cent. The patient was unable to remain under observation at the time, but on September 12 he returned. The basal metabolic rate was +30 and +26 per cent on two occasions. There were frank clinical evidences of exophthalmic goiter. Ten drops of compound solution of iodine was given three times a day. On September 24 the basal metabolic rate was

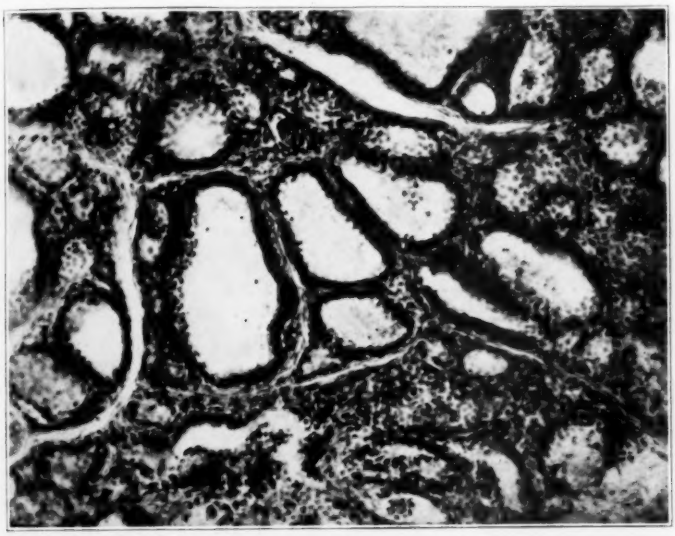

Fig. 4.—Hypertrophic parenchymatous thyroid tissue.

+14 per cent, and there had been a definite improvement in the patient's condition. On September 26 partial thyroidectomy was performed, and 18 Gm. of tissue was removed, leaving an amount of the posterior part of each lobe equal to about a fourth of a normal-sized lobe. Pathologic examination of the excised portions of gland revealed colloid thyroid tissue (fig. 3).

The patient was seen again on November 18. He had felt perfectly well until two weeks previously, when he had again noted nervousness, insomnia, headache in the frontal region and abnormal stimulation. The remnant of thyroid gland was not palpable. There was slight tremor of the fingers, and the skin was warm and moist. The blood pressure was 142 systolic and 90 diastolic and the pulse rate 94. The basal metabolic rate was +12 and +11 per cent on two occasions. Iodine was again given, and by December 6 the basal metabolic rate had gradually fallen to —2 per cent, with subsidence of symptoms. After this the patient took iodine irregularly, and on Jan. 5, 1931, the basal metabolic rate had risen to +8 per cent,

and there was clinical evidence of hyperthyroidism. The condition was again controlled by the regular use of iodine, and the basal metabolic rate was reduced to —5 per cent. From then until September 17 the patient's condition varied from time to time. On several occasions there were evident exacerbations of hyperthyroidism, with the basal metabolic rate as high as +22 per cent. There seemed to be gradually increasing evidence of hyperthyroidism over the entire period. Compound solution of iodine was taken during most of this time. In September and October 1931 three courses of roentgen treatment over the thyroid gland were given. There seemed to be no apparent benefit from this, but the amount of treatment was not great. On November 17 the patient was bothered so much by symptoms of hyperthyroidism that he decided to follow the advice previously given to have another portion of the thyroid gland removed. The last previous determination of the basal metabolic rate had been made on October 29 and was +13 per cent. At operation the right lobe was observed to be about a fourth and the left lobe about a fifth as large as a normal lobe. Very small bits of thyroid tissue were removed from each lobe and from the left lateral wall of the trachea. Glandular tissue amounting to about an eighth or a tenth of a normal-sized lobe was preserved on the left side, and tissue amounting to about a fifth of a normal-sized lobe was preserved on the right. The tissue removed weighed 1 Gm. and was reported pathologically as hypertrophic parenchymatous thyroid tissue (fig. 4). The basal metabolic rate was determined frequently, the dates and results being as follows: November 23, +19 per cent; November 25, +12 per cent; November 30, +9 per cent; December 5, +2 per cent, and Jan. 25, 1932, —8 per cent. At the time of the last test the patient felt perfectly well and had no clinical evidence of hyperthyroidism.

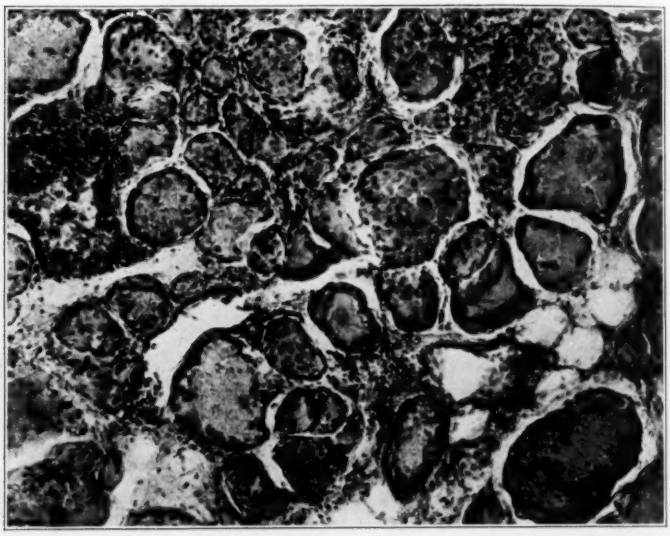

Fig. 5.—Colloid thyroid tissue.

In May 1932 the patient was again examined. At that time he said he had been nervous, had had palpitation and had lost 5 pounds (2.3 Kg.) during the previous two months. The basal metabolic rate was +2 per cent. He was still taking compound solution of iodine and was advised to continue doing so. In September 1932 he wrote that his health was excellent. His health continued to be good until April 1934, when he suddenly dropped dead. Permission for necropsy was not obtained.

Case 3.—A woman aged 51 was seen first on March 1, 1932. She gave a history of hyperthyroidism of fluctuating intensity for twenty months. During that time she had had a basal metabolic rate varying from +40 to +60 per cent, and she had taken iodine intermittently throughout the period of illness. The thyroid gland could not be outlined definitely. There were marked tremor and weakness

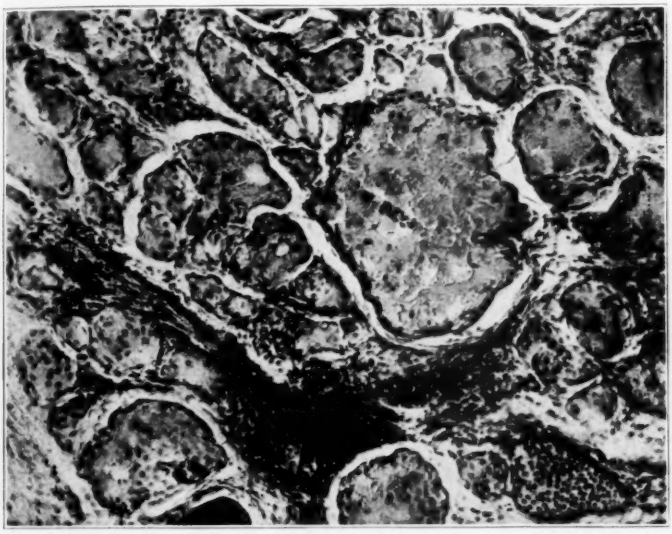

Fig. 6.—Colloid thyroid tissue with evidence of thyroiditis.

of the quadriceps muscles. The blood pressure was 138 systolic and 76 diastolic and the pulse rate 118. The basal metabolic rate was +50 and +43 per cent on two occasions. During treatment with iodine the basal metabolic rate dropped to +18 per cent, and a gain in strength and a reduction of nervousness were noted. On March 15 partial thyroidectomy was performed. The gland did not look like the usual exophthalmic goiter. Three grams of tissue was removed, and the pathologic examination revealed that it was from a colloid thyroid gland (fig. 5). On March 19 the basal metabolic rate was +7 per cent, and the patient's condition was improving.

On April 17, 1933, the patient returned to the clinic. For one month after her postoperative dismissal her condition had improved steadily. Then she had noted a recurrence of the tremor and had lost weight and strength. Iodine had been taken intermittently. The skin was hyperemic and moist. Marked tremor of the

fingers and weakness of the quadriceps muscles were noted. The blood pressure was 138 systolic and 82 diastolic and the pulse rate 140. No thyroid tissue could be felt. While the patient was at rest in the hospital the pulse rate varied from 93 to 116 beats per minute. At three consecutive tests the basal metabolic rate was +21, +12 and +7 per cent. The picture was frankly that of recurrent exophthalmic goiter. Compound solution of iodine, 10 drops three times daily, was prescribed, and the patient returned home temporarily. On June 5 she reentered the hospital. She had noted a moderate improvement in her condition. The blood pressure was 142 systolic and 92 diastolic and the pulse rate 120. Weakness of the quadriceps muscles, which had previously been graded 4, was now graded 2 plus. The clinical evidences of hyperthyroidism seemed definite. Only one test of the basal metabolic rate was made, as the patient had decided to undergo further resection of the thyroid gland and did not wish to delay it; this rate was +34 per cent and was probably not basal, as the patient was very nervous. The operation was performed on June 6. Very small remnants of thyroid tissue were observed on both sides of the trachea. About half the thyroid tissue was removed, and the right inferior thyroid artery was ligated. The fragments of tissue removed revealed the presence of a colloid thyroid gland with evidences of thyroiditis

Determinations of the Basal Metabolic Rate, Blood Pressure and Pulse Rate in Case 3

1933	Basal Metabolic Rate, Percentage	Blood Pressure		Pulse Rate
		Systolic	Diastolic	
June 13	+12	124	68	96
June 16	+ 4	112	70	89
June 19	— 4	120	78	91
June 23	— 8	110	80	75

(fig. 6); they weighed less than 1 Gm. Subsequent observations of the basal metabolic rate, blood pressure and pulse rate are given in the accompanying table.

During this time there was a gain in weight of 7 pounds (3.2 Kg.). The patient was much more quiet, the skin became cooler and less moist and the tremor diminished. The strength increased rapidly, and the weakness of the quadriceps muscles at the time of the patient's dismissal was graded 1 plus.

In a letter dated Sept. 19, 1933, the patient reported a continuous and marked improvement in general health and stated that she could do much more without fatigue. The basal metabolic rate taken at home was reported as —24 per cent. In January 1934 she lost weight, and the pulse rate increased. She was reported to have a basal metabolic rate of +51 per cent. However, by the first part of February she was again improving, and the basal metabolic rate was reported to be normal. In June 1934 the patient was again examined. The basal metabolic rate was —11 per cent, and there was no clinical evidence of thyroid disturbance.

COMMENT

The first patient presented at the time of the recurrence a much more severe degree of intoxication than would have been anticipated from the amount of thyroid tissue remaining. At first certain hysterical features made us doubt the accuracy of the basal metabolic tests, but the clinical

manifestations of exophthalmic goiter were sufficiently characteristic to overcome that doubt. The second operation was postponed for a long time in the hope that there would be a subsidence in the intensity of the disease. The relief from symptoms which occurred within a week of operation was striking, and the beneficial effects of the second resection were unquestionable. At the time of dismissal the patient emphatically stated that she was in better health than she had been for years. Her opinion was corroborated when the basal metabolic rate had been brought to normal after the treatment of myxedema.

The second patient probably had had mild hyperthyroidism at times since the second operation; but this condition apparently had subsided, and the patient's health was good until the time of his death, two and a half years after the last operation, from causes apparently not associated with thyroid disease. This patient was being seen at the time the result of the second thyroidectomy in case 1 became evident, and this encouraged us in advising a second resection in case 2 also. Case 3 corresponded to the other cases except that evidence of parenchymatous hypertrophy was not observed in the thyroid tissue removed at either of the two operations.

Phemister and Delaney [2] have reported a case which was similar in some respects to our case but in which no thyroid tissue was identified at necropsy.

The three cases reported are of special interest because of the very small amount of thyroid tissue observed at the time of the second operation and because of the excellent results obtained by further resection. As only 1 Gm. or less of thyroid tissue was removed in each case, the question naturally arises whether a secondary operation would have been necessary in these cases if a gram more of tissue had been removed originally. The answer is not known, but it is our opinion that this procedure would not necessarily have prevented recurrence of hyperthyroidism; furthermore, we are convinced that it is still possible for the two surviving patients, who now have only a minute amount of thyroid tissue, to have further recurrence of the disease.[3] In other words, after subtotal thyroidectomy for exophthalmic goiter, in which 65 to 85 per cent of the tissue is removed, the degree of activity of the remaining portion of the gland is dependent not wholly on the size of the gland but rather, and to an important extent, on the persistence or recurrence of the stimulus that originally produced the disease. There

2. Phemister, D. B., and Delaney, P. A.: Thyrotoxicosis Continuing After Extreme Operative, Iodine and Roentgen Therapy, J. A. M. A. **100**:586 (Feb. 25) 1933.

3. Pemberton, J. deJ: Recurring Exophthalmic Goiter: Its Relation to the Amount of Tissue Preserved in Operation on the Thyroid Gland, J. A. M. A. **94**:1483 (May 10) 1930.

is clinical and pathologic evidence to indicate that after subtotal thyroidectomy there follows in a large proportion of cases actual subsidence of the disease rather than abatement of the symptoms alone.

SUMMARY

Three cases are presented in which recurrence of exophthalmic goiter occurred when the remaining amount of thyroid tissue was so small as not to be palpable. In none of these cases was control of hyperthyroidism achieved by the administration of compound solution of iodine. A second operation in each case revealed such a small amount of thyroid tissue that not more than 1 Gm. could be removed. Control of hyperthyroidism was accomplished in each case after the removal of this small amount of tissue.

GENERALIZED DISCOLORATION OF SKIN RESEMBLING ARGYRIA FOLLOWING PROLONGED ORAL USE OF BISMUTH

A CASE OF "BISMUTHIA"

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Argyria is so striking a condition that its recognition is easy. Usually the diagnosis is made by inspection alone. Recently a patient with a deep blue discoloration of the skin and mucous membranes entered ward 15 of the Cook County Hospital complaining of severe diarrhea. At first the condition was considered to be argyria, but when the patient was questioned the possibility of bismuth poisoning appeared. A number of years before the patient had been told that he had a peptic ulcer. He thought the medicine given at that time was silver nitrate. Later diarrhea appeared. It had persisted for eighteen years, during which time he had ingested large amounts of bismuth salts.

Since large amounts of the less soluble bismuth compounds have been given orally to patients in the past without fear, this case seemed unusual. Histologic and chemical studies of the skin definitely excluded silver and established bismuth as the cause of the pigmentation. No mention has been found in the available literature of permanent generalized discoloration of the skin and the mucous membranes. The term "bismuthia" is suggested for the condition.

REPORT OF CASE

History.—J. H., a white man born in Tennessee, entered the Cook County Hospital complaining of abdominal distress, occasional vomiting and diarrhea, for the past eighteen years. In 1916 he fell 52 feet (15.8 meters) from a scaffolding on which he had been doing carpenter work. He was picked up semistuporous

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and taken home and was confined to his bed for eighteen months. A short but undetermined time prior to the accident, diarrhea appeared, which had been constantly present. He had from two to ten movements daily, the stools frequently containing mucus and pus and rarely small amounts of blood. When they were first noted, these frequent watery discharges were controlled by a mixture of 20 grains (1.2 Gm.) of bismuth subnitrate and sufficient camphorated tincture of opium to make 1 drachm (4 cc.). He complained of intermittent gnawing pains, griping attacks of colic and vomiting. Relief from these symptoms was

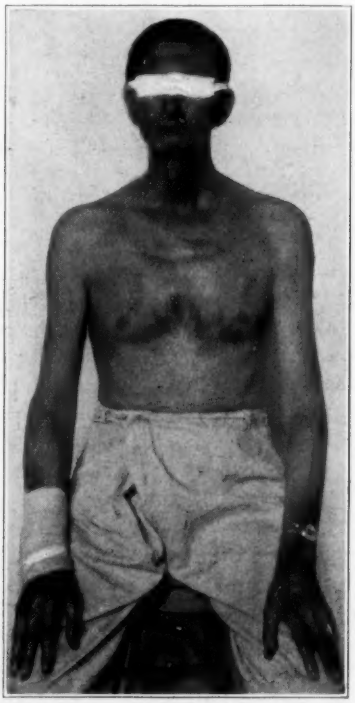

Fig. 1.—Photograph of the patient, showing the unevenness of the pigmentation.

attained by the continual use of the aforementioned mixture; often as much as 4 ounces (120 cc.) daily was needed. During February 1918, while he still had fair skin and very light reddish hair, he began to notice a steel-gray discoloration. Only three days later, to use the patient's words, "I turned the color I have been ever since." Subsequent to this, various other compounds of bismuth, such as the subcarbonate, the subgallate and the oxide, were used in amounts of from 10 to 30 grains (0.6 to 2 Gm.) per dose. Despite his discomfort he managed to maintain his body weight until four months before his second admission.

There was a hemorrhoidectomy in 1916. The patient had had chronic alcoholism for fifteen years prior to admission.

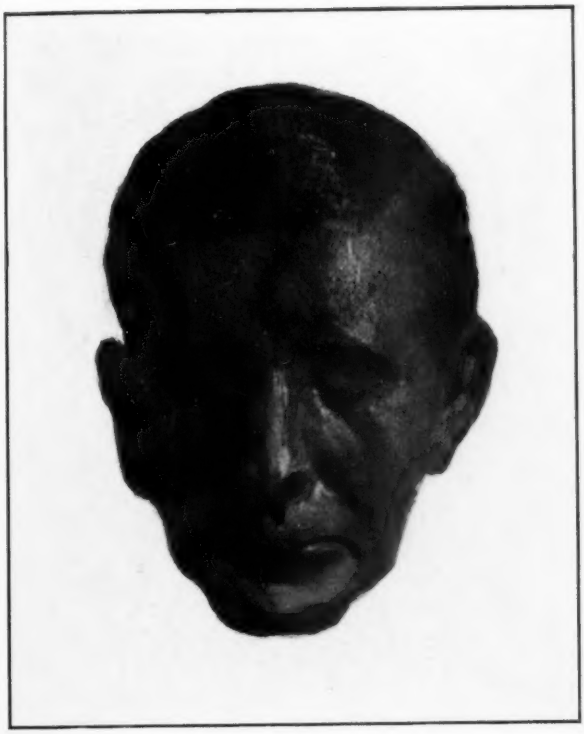

Fig. 2.—Portrait of the patient painted from life.

General Examination.—The patient was slender and slightly emaciated, and his skin was colored deep blue-gray, with a distinct metallic sheen. The hair was thin and of fine texture, with a deep mahogany shade. Both pupils were round and regular and reacted to light and in accommodation, but the somber gray conjunctiva gave the eyes a glassy, cadaveric appearance. All the teeth had been removed, and the buccal and pharyngeal mucous membranes were a deep indigo-purple-black. Neither the cervical glands nor the thyroid gland were palpable. The patient was of the asthenic habitus, with a long, thin, symmetrical chest; the lungs and the heart were essentially normal except for the accentuated aortic second tone. The blood pressure was 152 systolic and 90 diastolic. Slight tenderness was elicited in the abdomen, especially in the epigastric region and the left lower quadrant. Rectal examination revealed internal and external hemorrhoids.

The discoloration of the skin was the most striking feature. It was a universal pigmentation, being most prominent and of the richest color over the forehead, face and neck and the dorsa of the hands (fig. 1). No description of the color of the face is adequate (fig. 2). As the result of burns, cuts and bruises, the dorsa of the hands were mottled with many light pearly-gray scars. The skin of the remainder of the body was of a drab, ashen hue, being lightest at the inner aspects of the thighs and over the scrotum.

Nothing abnormal was found in the urine or in the blood chemistry, and a negative Kahn reaction was recorded. Secondary anemia was present, with 2,680,000 red blood cells and a hemoglobin content of 70 per cent, while there were 7,900 leukocytes per cubic millimeter. Roentgenographic and fluoroscopic examination of the duodenum showed an ulcer, but the rest of the gastro-intestinal tract was normal. A mixture of 6 per cent sodium thiosulfate and 0.66 per cent potassium ferricyanide in distilled water was injected as superficially as possible in the skin over the right trochanter. Immediate blanching of the skin about the site of injection followed this modification of the Stillians and Lawless test.[1] Under these conditions, patients with argyria show a similar blanching of the skin.

Nearly one year later he entered the hospital with impending delirium tremens. After three days he was much improved; however, he continued to have a low grade fever. A roentgenogram of the chest showed marked infiltration of the upper third of the left lung field, which in addition to the clinical findings assured the diagnosis of ulcerocaseous tuberculosis.

Histologic Examination.—A specimen of the skin was taken for biopsy from the dorsum of the right hand, where the pigmentation was very deep. Microscopic examination showed innumerable small granules of a metallic nature in the capillary and reticular layers of the dermis (fig. 3).

Chemical Examination of the Skin for Bismuth.—A piece of skin 4.5 by 2.5 cm. was removed from the area overlying the left greater trochanter. It was placed in a new clean sillimanite dish and ashed in an electric muffle furnace at 500 C. (± 10 C.) for eighteen hours. The ash was a pale cream-white powder. Any mercury that might have been present would have been volatilized by this treatment. The ash was moistened with dilute nitric acid and evaporated on a steam bath until almost dry; then a small amount of dilute hydrochloric acid (5 per cent) was added. This was allowed to remain on the steam bath for several hours, after which it was filtered through a fine-grained filter paper. Any silver present in the tissue would have been converted by this procedure to silver chloride,

1. Stillians, A. W., and Lawless, T. K.: The Intradermal Treatment of Argyria, J. A. M. A. **92**:20 (Jan. 5) 1929.

which would then remain as a residue on the filter paper. The filtrate was clear and free from opalescence. After the filter paper was washed with hot water, it was extracted with a warm dilute solution of ammonium hydroxide. The extract after filtration was rendered acid to litmus by the addition of dilute hydrochloric acid. No opalescence or precipitate formed. This showed absence of silver.

The filtrate obtained from the treatment with hydrochloric acid would be expected to contain other metallic salts. It was placed in a small evaporating dish, and 2 cc. of concentrated sulfuric acid was added. It was then evaporated slowly on an electric hot plate until fumes of sulfur tri-oxide were evolved. After cooling, the contents of the dish were diluted by the addition of 100 cc. of water and 100 cc. of 95 per cent ethyl alcohol and allowed to stand overnight. The absence of a precipitate at that point indicated that lead was not present. The filtrate was evaporated to a volume of 100 cc., placed in an Erlenmeyer flask and

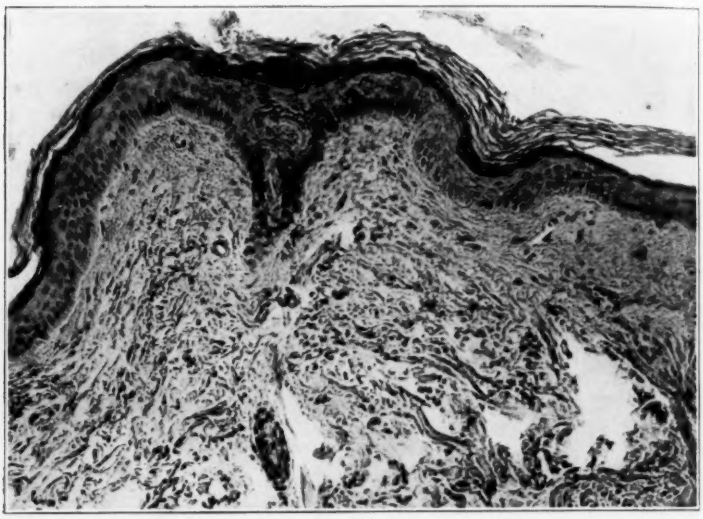

Fig. 3.—Photomicrograph of a section of the skin. There are many small metallic granules in the capillary and reticular layers.

saturated with hydrogen sulfide gas. A small amount of dark brown, somewhat flocculent precipitate formed. After standing overnight the solution was again saturated with hydrogen sulfide and filtered. The filter paper containing the brown precipitate was washed first with distilled water which had been saturated with hydrogen sulfide and then with warm, freshly filtered ammonium polysulfide solution (to remove any traces of arsenic, antimony or tin) and finally with a saturated solution of hydrogen sulfide in water. The dark brown sulfide precipitate which remained was readily soluble in warm dilute hydrochloric acid. This acid solution was carefully evaporated in a small sillimanite dish on a steam bath until just dry. The faint crust of residue was white and when moistened with a drop of ammonium hydroxide it gave no trace of blue coloration (absence of copper). This indicated that the sulfide was that of bismuth. The residue was barely acidified with hydrochloric acid and again precipitated by the addition of cold water which had been

saturated with hydrogen sulfide. By comparison of the intensity of the dark color produced by this precipitate with that obtained from known amounts of bismuth, the quantity present was estimated to be 0.05 mg. (± 0.01 mg.).

Chemical Examination of the Urine for Bismuth.—The presence of bismuth in the skin raised the question of bismuth in circulation. Two twenty-four hour specimens of urine were collected from the patient, evaporated to dryness, ashed and tested for bismuth by means of the quinine potassium iodide reaction of Aubry.[2] These tests gave negative results for bismuth.

COMMENT

It is generally assumed that the less soluble salts of bismuth taken by mouth are harmless, yet a number of deaths from bismuth poisoning have been reported. The exact mode of death was not always the same. Impurities, such as arsenic,[3] zinc and lead,[4] the results of improper manufacture and purification of the bismuth salts, caused many fatalities. Some blamed the cations,[5] while a few held the metal responsible.[6] The experiments of Böhme were conclusive and classic.[7] He found that bismuth subnitrate when mixed in a test tube with feces from human beings (particularly of children) liberated nitrites. Early death after the ingestion of large amounts of bismuth subnitrate simulated that caused by poisoning with sodium nitrite. In both cases there were an acute onset, increasing dyspnea, methemoglobinemia and death. Thus, he concluded, poisoning from bismuth subnitrate was really a nitrite phenomenon. Since then methemoglobinemia has been frequently demonstrated, and recently Roe [8] reported the death of a 1 month old infant who had been given 190 grains (13 Gm.) of bismuth subnitrate.

In a few cases intoxication followed the use of dusting powder containing bismuth salts. As early as 1882 Kocher [9] reported cases of

2. Aubry, P.: Recherche du bismuth dans l'urine, J. de pharm. et chim. **25:** 15, 1922.

3. (*a*) Goadby, Kenneth: Diseases of the Gums and Oral Mucous Membranes, ed. 4, New York, Oxford University Press, 1931, p. 356. (*b*) Fullerton, H. S.: Case of Poisoning by Impure Nitrate of Bismuth, Am. J. M. Sc. **67:**280, 1874. (*c*) Salisbury, J. H.: Arsenic in Subnitrate of Bismuth, Chicago M. J. & Exam. **36:**601, 1878.

4. Webster, R. W.: Legal Medicine and Toxicology, Philadelphia, W. B. Saunders Company, 1930, p. 475.

5. Schumm: Spektroskopischer Nachweiss der Bismuthum subnitricum Vergiftung, Deutsche med. Wchnschr. **36:**1250, 1910.

6. Lewin, L.: Ueber Wismutvergiftung und einen ungiftigen Ersatz des Wismuths für Röntgenaufnahmen, München. med. Wchnschr. **56:**643, 1909.

7. Böhme, A.: Ueber Nitrivergiftung nach interner Darreichung von Bismuthum subnitricum, Arch. f. exper. Path. u. Pharmakol. **57:**441, 1907.

8. Roe, H. E.: Methemoglobinemia Following the Administration of Bismuth Subnitrate: Report of a Fatal Case, J. A. M. A. **101:**352 (July 29) 1933.

9. Kocher, T.: Ueber die einfachsten Mittel zur Erzielung einer Wundheilung durch Verklebung ohne Darmröhren, Samml. klin.Vortr. no. 224, 1882 (Chir. no. 72), p. 1917.

stomatitis, progressing to ulceration, diphtheritic gingivitis, dysphagia, nephritis, nausea and diarrhea, following the use of bismuth subnitrate as a dusting powder on freshly granulating wounds. One patient who came to autopsy had large purple areas of ulceration throughout the mucous membranes of the colon and the terminal portion of the ileum.

Mixtures of salts of heavy metals and petrolatum were used by surgeons about thirty years ago to obliterate sinuses and troublesome cavities, again drawing attention to bismuth. In 1909 Beck [10] stressed the dangers of his paste (a bismuth-petrolatum mixture containing 33 per cent of bismuth subnitrate). Severe toxic reactions occurred in three of his patients. "In many cases I have noted a slight lividity of the mucous membranes of the skin and a bluish border at the margin of the teeth; otherwise conditions were perfectly normal." The nausea, vomiting and albuminuria which followed the use of his paste gradually disappeared after its removal. He warned that not more than 100 Gm. of the paste should be used in any case, suggesting that a reduction of the 33 per cent bismuth subnitrate content be made when larger quantities of the paste were necessary. A few years later he was able to report eleven cases in which the patient was treated with the paste, but in 30 per cent of them there was pigmentation of the gums.[11] In a later series of 1,800 cases without a fatality,[12] he curiously enough gave specific direction for the prompt removal of the paste by oil when toxic symptoms arise. A Negro into whose thorax 1,250 cc. of the paste had been injected to obliterate an empyema cavity was reported by Higgins [13] to have shown signs of bismuth poisoning within two weeks after the operation. The evacuation of the bismuth paste resulted in the prompt healing of the oral lesions, but the steel-blue line along the borders of the gums persisted.

Many cases of toxic reactions from the paste were observed. Six of twenty-five orthopedic patients requiring treatment in the Cook County Hospital who were treated with Beck's paste showed blue lines on their gums. Less than 10 ounces (311 Gm.) of the mixture had been given to four of these patients.[14] David and Kauffman, working

10. Beck, E. G.: Toxic Effects from Bismuth Subnitrate, with Reports of Cases to Date, J. A. M. A. **52**:14 (Jan. 2) 1909.

11. Beck, E. G.: The Surgical Treatment of Tuberculous Sinuses, Tr. Internat. Cong. Tuberc. **2**:219, 1908.

12. Beck, E. G.: Bismuth Paste in Chronic Suppurative Sinuses and Emphysema, J. A. M. A. **67**:21 (July 1) 1916.

13. Higgins, W. H.: Systemic Poisoning with Bismuth, J. A. M. A. **66**:648 (Feb. 26) 1916.

14. David, V. C., and Kauffman, J. R.: Bismuth Poisoning: Two Cases, with One Fatality, Following Injection of Bismuth-Vaselin Paste, J. A. M. A. **52**:1035 (March 27); 1953 (June 12) 1909.

under the direction of Prof. Walter S. Haines, were able to detect bismuth in excised bits of the affected mucous membranes. Cabot [15] and Warfield [16] each reported fatalities from the use of Beck's paste. Mayer and Baehr in their clinicopathologic studies of bismuth poisoning in 1912 found reports of seventy cases and twenty-six deaths in the literature.[17] Since then, pigmentation of the mucous membranes and the blue line of the gums have been frequently mentioned. They followed the use of bismuth pastes, particularly a bismuth-iodoform-paraffin paste.[18]

The use of bismuth compounds as spirocheticides again directed attention to the pharmacology of this drug. Most of the work is concerned with the rate of absorption and excretion of the various bismuth preparations (chiefly the soluble ones given intramuscularly). An excellent review of this subject is that of von Oettingen.[19] A majority of those infrequent dermatoses following the intramuscular injections of bismuth salts are reported in the French literature. Erythroderma and scarlatiniform, hemorrhagic, urticarial and exfoliative lesions have been described. Less frequently herpes zoster and lesions resembling erythema multiforme occurred, while chronic forms resembled eczematous and maculosquamous eruptions. Exfoliative lesions are reported frequently, but the concomitant use of arsenical compounds divides the blame. Skolnik and Aleshire,[20] working in a large clinic, found only twenty-two cases of dermatitis caused by bismuth after a three year study during which more than 25,000 intramuscular injections of bismuth had been given. The lesions they observed regressed to normal on the abstinence from further treatment, only to reappear when the injections were resumed. The acute lesions in general resembled pityriasis rosea, while the chronic ones simulated lichenified dermatitis. These

15. Cabot, R. C.: Bismuth Poisoning, with a Report of a Case, Tr. A. Am. Physicians **27**:457, 1912.

16. Warfield, L. M.: Bismuth Poisoning, Am. J. M. Sc. **144**:647, 1912.

17. Mayer, L., and Baehr, G.: Bismuth Poisoning, Surg., Gynec. & Obst. **15**: 309, 1912.

18. Morison, R.: The Treatment of Infective Suppurative War Wounds, Brit. J. Surg. **4**:659, 1917. Phillips, J.: Bismuth Poisoning and Nitrite Poisoning from the Use of Bismuth Subnitrate with a Report of Three Cases, Cleveland M. J. **16**: 419, 1917. Hepworth, F. A.: Toxic Symptoms After the Use of Bismuth Paste, Lancet **1**:573, 1917. Blight, F. J.: Bismuth Poisoning as Affecting the Oral Cavity, Brit. Dent. J. **38**:940, 1917. Wheeler, W. I. de C.: Pigmentation from Bismuth Absorption After the Use of B. I. P. P. (Bismuth Iodoform Paraffin Paste), Brit. J. Surg. **18**:329 (Oct.) 1930. Goadby.[3a]

19. von Oettingen, W. F.: The Absorption, Distribution and Excretion of Bismuth, Physiol. Rev. **10**:221 (April) 1930.

20. Skolnik, E. A., and Aleshire, I.: Skin Eruptions from Bismuth Therapy in Syphilis, J. A. M. A. **98**:1798 (May 21) 1932.

closely resembled those blotchy macular eruptions that had been noted occasionally after the use of dusting powders containing bismuth.[21] Several years ago we observed a tabetic patient in ward 15 of the Cook County Hospital who had a deep blue discoloration of the entire oral mucosa after intensive intramuscular bismuth medication. Despite this treatment a Charcot knee slowly developed.

A variety of animals have been used to study the poisonous effects of bismuth salts. Steinfeld and Meyer [22] in their study of the toxicity of subcutaneous injections of bismuth oxide in frogs, cats, rabbits and dogs found two kinds of reaction. Acute poisoning characterized by rapid respiration, bradycardia, convulsions and death was seen after a few hours. Chronic intoxication was manifest by stomatitis, salivation, diarrhea, anorexia, necrosis and ulceration of the colon. Many have reported similar results after the injection of bismuth compounds, whereas oral administration was presumed to be nontoxic. Susceptibility varied. Dogs and rabbits tolerated large amounts, while cats were poisoned by small doses of bismuth subnitrate.[23] Dalché, however, first described the bismuth line.[24] He mentioned a brown glistening line on the gums of the anterior molars and the inferior maxilla, with dark violet spots in the mucosa of the left cheek.

The first attempt to demonstrate the presence of bismuth in an animal poisoned by its salts by the use of microchemical methods was made by Schmelzer.[25] The results were not conclusive. Since then bismuth has been isolated from practically every organ of the body, except the skin, of poisoned rabbits [26] and human beings.[27] The kidneys, liver and lungs seem to harbor the largest amounts.

Most of the work on the absorption of bismuth has been done after intramuscular or intravenous injections; however, Bargen, Osterberg

21. Dorn, L. W.: Ueber Dermatolvergiftung, Beitr. z. klin. Chir. **70**:155, 1910. Windrath: Ueber Wismut-Intoxikation: Nebst Mitteilung eines tödlich verlaufenden Falles nach Application einer Bi-Salbe, Med. Klin. **6**:742 (May 8) 1910.

22. Steinfeld, W., and Meyer, H.: Untersuchungen über die toxischen und therapeutischen Wirkungen des Wismuts, Arch. f. exper. Path. u. Pharmakol. **20**:40, 1885.

23. Nowak, J., and Gütig, C.: Nitritvergiftung durch Bismuth subnitricum, Berl. klin. Wchnschr. **45**:1764, 1908.

24. Dalché, P., and Villejean, E.: Recherches expérimentales sur la toxicité du bismuth, Arch. gén. de méd. **2**:129, 1887.

25. Schmelzer, W.: Studie über den pathologisch-anatomischen Befund bei der Wismutvergiftung, Jurjew, Schnakenburg, 1896.

26. Leonard, C. S.: Tissue Distribution of Bismuth, J. Pharm. & Exper. Therap. **34**:333, 1928.

27. Munch, J.: Wismuthvergiftung mit tödlichen Ausgang, Dermat. Wchnschr. **84**:367, 1927. Mayer and Baehr.[17]

and Mann [28] found that soluble bismuth salts were readily absorbed by the colon. There is ample evidence to show that bismuth is circulated through the body and that the intensity of excretion is determined chiefly by the concentration of the plasma.[29] Single doses are easily absorbed and excreted, but after successive doses there seems to be a delay in its excretion.[30] In fact, after intensive medication the accumulation of bismuth supervenes.

Only the insoluble bismuth salts were used in our case. There are two possible explanations for the observed pigmentation: Either these salts had been ingested over an unusually long period of time (eighteen years) or the chronic ulceration of the colon had altered the rate of absorption. It is assumed that the prolonged use of the salts caused an excessive accumulation of bismuth in the blood plasma and its deposition in the tissues of the body in a fairly insoluble form, much as occurs in argyria.

Pigmentation of the mucous membranes of the mouth and tongue has frequently been described. A Leitz capillary microscope has been used to study the histopathologic characteristics of the deposits.[31] A similar discoloration has been observed in the urinary bladder of a patient receiving a course of bismuth as a part of his antisyphilitic treatment.[32] Our sections show microscopic features identical with these. Melanosis coli following the use of bismuth has almost the same microscopic picture. It is interesting to note that in two of the three cases of this condition described by Micseh [33] it was associated with pulmonary tuberculosis, as in our case.

A rough though inaccurate estimate of the amount of bismuth in the skin of the entire body was made by means of the Du Bois table for surface area. The skin used in our biopsy was taken from one of the lightest areas; on the basis of its analysis about 82 mg. of bismuth was calculated to have been present in the entire skin.

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28. Bargen, J. A.; Osterberg, A. E., and Mann, F. C.: Absorption and Excretion of Arsenic, Bismuth and Mercury: Experimental Work on the Colon, Am. J. Physiol. **89**:640, 1929.

29. Sollmann, T.; Cole, H. N., and Henderson, K. I.: Excretion of Bismuth in a Series of Clinical Bismuth Treatments, Arch. Dermat. & Syph. **28**:615 (Nov.) 1933.

30. Hanzlik, P. J., and Mehrtens, H. G.: Comparative Excretion and Absorption of Different Bismuth Products: Summary Reports, Arch. Dermat. & Syph. **22**:861 (Nov.) 1930.

31. Löhe, H., and Rosenfeld, H.: Untersuchungen über Wismutsaum und seiner Beziehungen zum Gesamtorganismus, Dermat. Ztschr. **50**:409, 1927.

32. Löhe, H., and Rosenfeld, H.: Wismuthpigmentierungen der Blasenschleimhaut, Dermat. Ztschr. **57**:250, 1929.

33. Micseh, G.: Wismuth Melanose der Dickdarmschleimhaut, Beitr. z. path. Anat. u. z. allg. Path. **92**:147, 1933.

SUMMARY

A case of generalized permanent discoloration of the skin resembling argyria is reported. The condition developed after the prolonged oral administration of bismuth salts. A method of chemical estimation of the amount of bismuth in the skin is described. The toxicology of bismuth salts is discussed briefly.

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TULAREMIC PNEUMONIA, PERICARDITIS AND ULCERATIVE STOMATITIS

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The mortality rate in 3,653 cases of tularemia reported in the United States up to 1933, according to Francis,[1] was 4.9 per cent. Simpson[2] in 1928 stated that the mortality rate in the United States was 3.7 per cent, but Foshay[3] expressed the belief that it is between 6 and 7 per cent. The records of Francis reveal that there are only three states, Connecticut, Maine and Vermont, in which cases of the disease have not been reported. Tularemia is prevalent in Japan and Russia. The occurrence of the disease has recently been reported in Canada, Norway, Sweden and Finland. In England tularemia has occurred only among laboratory workers. Thus, contrary to the general opinion, tularemia, among the infectious diseases, has a relatively high mortality rate and is rather widespread.

Although the literature concerning tularemia is rapidly increasing, there remains much to be elucidated. The causative organism is poorly understood; its disseminating propensities within the human body are not clear; the few descriptions of the histopathologic picture are apparently incomplete and contradictory, and the very promising specific therapy discovered by Foshay has not been given the deserved attention. Thus, three fields, bacteriology, pathology and specific therapy, beckon the investigator toward further exploration. Nevertheless, comparatively few investigators have undertaken the study of this disease. This is proved by the fact that after approximately twenty years of observation of the disease in man specific antiserum "escaped the usual trials" until Foshay[4] introduced it in 1932. Bacterium tularense has been known for twenty-five years, yet the motility of this organism has only recently been observed by Ohara[5] and with uncertainty by me. The

From the Department of Clinical Pathology, St. Mary's Hospital, and the Wisconsin State Laboratory of Hygiene.

1. Francis, E.: Tularemia, Am. J. Nursing **34**:1, 1934.
2. Simpson, W. M.: Tularemia (Francis Disease), Ann. Int. Med. **1**:1007, 1928.
3. Foshay, Lee: Personal communication to the author, 1935.
4. Foshay, Lee: Serum Treatment of Tularemia, J. A. M. A. **98**:552 (Feb. 13) 1932; Tularemia Treated by a New Specific Antiserum, Am. J. M. Sc. **187**:235, 1934; On the Treatment of Tularemia, Ohio State M. J. **31**:21, 1935.
5. Ohara, cited by Foshay.[3]

task of elucidating the histopathologic picture of tularemia is difficult because the necropsy material is deplorably meager and widely scattered. No comprehensive study has been published. Necropsy has been performed in less than 10 per cent of the fatal cases of tularemia. Gundry and Warner [6] in 1934 summarized the results of necropsy in all cases reported in this country, including their own (the fifteenth case). They purposely omitted Breucken's case, reported by Francis and Callender,[7] because the patient died of streptococcic septicemia about five months after the onset of tularemia. They failed to include the cases of Haizlip and O'Neil,[8] Gudger [9] and Hartman, Beaver and Green.[10] Beck and Merkel [11] reported a case in 1935. Thus 20 cases of tularemia in which necropsy was performed have been reported in this country at the time this paper is written.

The purpose of this presentation is to stimulate physicians to make more postmortem observations in fatal cases of tularemia and to report the clinical and postmortem studies in unusual cases. It must be emphasized that if the present knowledge of the pathologic process of tularemia is to be improved it will be necessary to increase the present percentage of necropsies that are performed in fatal cases. Foshay and others are anxious for all fatal cases to be reported in the literature. I urge those who have studied this disease post mortem to submit their studies for publication.

The following case is the twenty-first reported in this country. It is perhaps the first case of tularemic pneumonia associated with tularemic pericarditis, ulcerative stomatitis and ulcerative glossitis observed at necropsy.

REPORT OF A CASE

J. S., a white woman aged 55, entered St. Mary's Hospital on Aug. 15, 1933, with a condition thought to be typhoid. Her chief complaints were severe diarrhea, severe pain in the abdominal region and fever.

She had been camping in the northern part of Wisconsin, along the bank of Lake Superior, two weeks prior to hospitalization. She attributed her illness to

6. Gundry, L. P., and Warner, C. G.: Fatal Tularemia: Review of Autopsied Cases with Report of a Fatal Case, Ann. Int. Med. **7**:837, 1934.

7. Francis, E., and Callender, G. R.: Tularemia: Microscopic Changes of the Lesions in Man, Arch. Path. **3**:577 (April) 1927.

8. Haizlip, J. O., and O'Neil, A. E.: A Case of Meningitis Due to Bacterium Tularense, J. A. M. A. **97**:704 (Sept. 5) 1931.

9. Gudger, J. R.: Tularemic Pneumonia: Report of a Case, J. A. M. A. **101**:1148 (Oct. 7) 1933.

10. Hartman, H. R.; Beaver, A. C., and Green, R. G.: The Occurrence of Tularemia in Minnesota in 1921: Report of Two Cases—One Fatal with Necropsy Report, Minnesota Med. **16**:559, 1933.

11. Beck, H. G., and Merkel, W. C.: Personal communication to the author, 1935.

drinking water from shallow wells and surface springs. While picking blueberries during the first day of camping, she was bitten two times on the right cheek by deer flies, and the following morning she removed three wood ticks from her legs. The areas bitten by the deer flies became swollen and angry red, and suppuration occurred. These areas healed rapidly without leaving a trace of their existence. The bites of the wood ticks caused no noticeable lesions. Two or three days later the patient felt weak and "feverish," and marked diarrhea developed. Thinking that she was afflicted with typhoid as a consequence of drinking surface water, she terminated her vacation and returned home. The temperature during the seven or eight days prior to hospitalization varied from 99 to 100 F. in the morning and from 103 to 104 F. in the afternoon.

The patient's temperature on her admission to the hospital (6 p. m.) was 104.2 F., the pulse rate 96 and the respiratory rate 26. Physical examination revealed no lesions on the external surface of the body. Several small grayish-white areas were present on the anterior two thirds of the dorsum of the tongue and on the mucosa of the right side of the lower gum. The abdomen was distended but not rigid; however, there were slight tenderness and definite muscular spasm in the entire right side of the anterior abdominal wall. There were no other positive physical signs. On the following day a trace of albumin was found in the urine. Examination of the blood revealed a normal chemical picture and 4,530,000 erythrocytes, 12,300 leukocytes and 82 per cent neutrophils, which showed a marked shift to the left and a toxic phase plus III. Nothing of note was found in the liquid feces, and the reaction to the benzidine test was negative. The blood serum did not agglutinate Bacillus typhosus, Bacillus paratyphosus, Brucella abortus and Bacterium tularense.

On August 17 the diarrhea subsided. A severe cough developed with expectoration. The tongue appeared dry and contained a few small grayish ulcers.

Small grayish-red ulcers were also present on the gums and on the mucosa of the right cheek. The heart tones were weak and the pulse rate was 115 and irregular and feeble. Moist râles were heard over all pulmonary areas, but they were more pronounced over the upper lobe of the left lung. The abdomen was slightly distended and was rigid and painful below the sternum. The blood culture and agglutination tests were negative.

On August 18 pericardial friction rubs were elicited, the pulse was normal and the temperature was 104 F. The sputum contained many epithelial cells, polymorphonuclear and lymphocytic leukocytes, pneumococci, staphylococci and very small coccoid gram-negative bacilli; no acid-fast bacilli were found.

On August 19 the patient coughed considerably. The expectorations were blood-streaked. She complained of severe pain in the area of the stomach and gall-bladder. Dulness and diminished breath sounds had developed over the upper part of the left lung. Loud friction rubs were heard over the cardiac area. The white cell count was 17,500. A blood culture and agglutination tests were negative.

On August 21 a flat roentgenogram of the chest showed the upper lobe of the left lung to be completely consolidated, and there were scattered consolidations throughout the lower lobe of the left lung (fig. 1).

On August 23 ascites developed. The veins of both lower extremities were dilated.

On August 26 a blood culture and agglutination tests were negative.

On August 30 (seventy-three days after the onset of the illness, including eight days of fever at home) the blood serum agglutinated Bact. tularense in a dilution of 1:320. Anemia and a slight degree of jaundice had been gradually developed. The erythrocytes numbered 3,290,000. A blood transfusion was performed.

On September 2 the patient's condition became critical. There was a persistent pronounced pericardial friction rub. The temperature was 103 F., the respiratory rate 40 and the pulse rate 128. Oxygen was given by a nasal catheter. Since admission the fever had been of the type noted in cases of typhoid.

After oxygen therapy was instituted, there was a break in the fever, so that by September 8 the temperature was 98 F., and during the following thirty-three days of life it remained between 97.8 and 98.8 F. Leukocytosis persisted with counts between 13,700 and 18,100. At times the patient seemed improved, but never enough to cause doubt as to the gravity of the prognosis. On various days she complained of soreness of the mouth, particularly of the tongue, pains in the abdominal region and dyspnea. She vomited several times. The ulcerations in the mouth remained the same. She coughed persistently; the expectorations decreased, and during the last ten days of life the cough was dry and very distressing. A flat roentgenogram of the chest made at the bedside revealed a

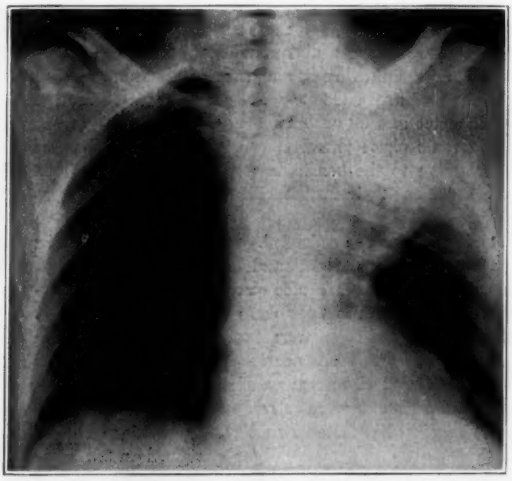

Fig. 1.—Roentgenogram showing consolidation of the upper lobe of the left lung.

marked pericardial effusion and pneumonia of the upper lobe of the left lung associated with effusion (fig. 2). Three hundred cubic centimeters of serosanguineous fluid was aspirated from the left side of the chest twelve hours before death. Death occurred on October 9, on the fifty-sixth day of hospitalization and sixty-four days after the onset of the illness.

The blood serum did not agglutinate Bact. tularense until the twenty-third day of the illness. Prior to the report of agglutination, the following clinical diagnoses were considered as the disease progressed: (1) typhoid, (2) acute cholecystitis, (3) pneumonia with pericarditis, (4) abscess of the lung, (5) miliary tuberculosis and (6) tularemic pneumonia.

The outstanding unusual manifestations in this case were as follows: (1) severe pains in the abdominal region, with diarrhea; (2) fever of the type present

in typhoid during the first thirty-six days of the illness, with a slow pulse rate; (3) normal and subnormal temperature during the last twenty-eight days of life, as shown in the temperature chart; (4) no lesions on the external surface of the body; (5) persistent leukocytosis and a constant pronounced shift to the left of the neutrophils; (6) mild jaundice; (7) lobar pneumonia with effusion; (8) pericarditis with effusion; (9) ulcerative stomatitis and ulcerative glossitis; (10) mild ascites, and (11) an increasing agglutination titer, which was suggestive on the twenty-first day, 1: 320 on the twenty-third day and 1: 5,120 on the sixty-fourth day.

Synopsis of Necropsy.—The skin and conjunctiva showed grade 1 icterus. The external surface of the body contained no gross lesions. There was no palpable lymphadenopathy. The mouth was dry. The dorsal surface of the anterior two thirds of the tongue contained several grayish-red shallow ulcers ranging from 0.5 cm. in diameter to 2 by 1.5 cm. The lower gum was also ulcerated and presented dirty gray accumulations at the alveolar borders. The

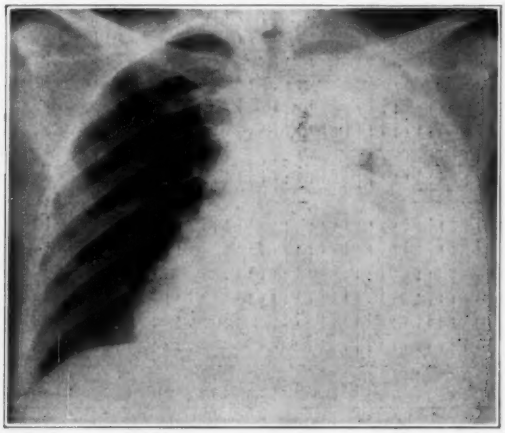

Fig. 2.—Roentgenogram showing pericardial effusion and pneumonia with effusion.

gum of the right side was very edematous. The mucosa of the right cheek was slightly edematous and contained three small grayish-white ulcerated areas. The subcutaneous veins of the anterior thoracic and abdominal walls were prominent and dilated. The right lower extremity below the knee had a grade 2 edema.

The rectus abdominis muscles contained brownish and light grayish-yellow areas. The abdominal cavity contained 550 cc. of unchanged serous fluid. The left pleural sac contained 2,100 cc. of serofibrinosanguineous exudate, and the right contained 500 cc. of similar but less fibrinous exudate. The mediastinal lymph nodes were massive, soft and edematous, and when they were sectioned some contained abscesses composed of a greenish-gray purulent exudate whereas others were involved with conglomerated areas of caseous necrosis. The pericardial sac was enormously dilated, measuring 18 cm. at the base and 17.5 cm. from the apex to the base. The pericardial sac contained 1,650 cc. of serosanguineous

exudate. The inner surface of the parietal pericardium and the epicardium were coated with thick ragged fibrinous membranes (fig. 4). The surface underneath the fibrinous layers was hyperemic. The heart measured 12 cm. at the base, and 11 cm. from the apex to the base. The right auricle and the right ventricle were dilated and filled with fluid and clotted blood. The myocardium was brownish red and contained grayish and yellowish areas. It was rather flabby but firm. The tracheobronchial lymph nodes showed changes similar to those seen in the mediastinum. Two of the lymph nodes containing abscesses were 3 cm. in diameter. The pleura of the left lung was coated with ragged grayish-yellow fibrinous membranes. The upper lobe was consolidated in its upper half, and various-sized nodules were felt in the lower half. The lower lobe was partly atelectatic. The visceral pleura overlying the consolidated portions stripped with ease, displaying yellowish-gray firm elevations and intervening depressed anemic pulmonary tissue. When the upper lobe was sectioned confluent lobular caseous pneumonia was seen

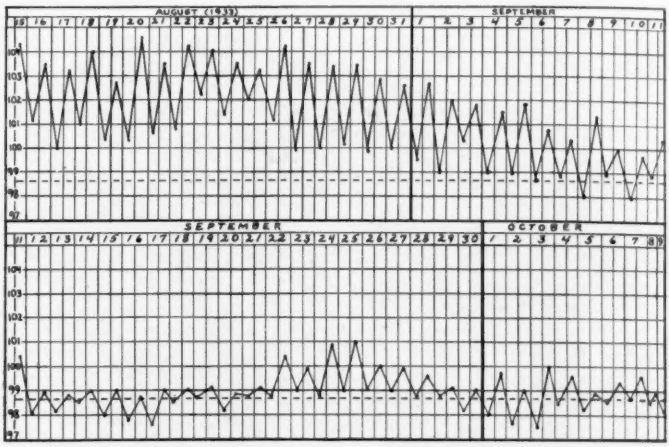

Fig. 3.—An unusual temperature record.

to involve the upper half, and the remaining half contained isolated and conglomerated tubercles ranging in size from 1 mm. to 1 cm. (fig. 5). The intervening pulmonary tissue in the areas of consolidation in the upper half of the upper lobe were depressed. The large area of confluent caseous consolidation closely resembled the changes seen in caseous tuberculous pneumonia and was quite unlike the appearance of gray hepatization in croupous pneumonia. The surfaces made by sectioning the lower lobe were dry, congested and atelectatic, and an occasional minute tubercle could be discerned. The upper lobe of the right lung was emphysematous, and the surfaces made by sectioning were dry and pale. The middle lobe contained two large hemorrhagic infarcts and thrombosis of the larger vessels. The spleen measured 13.5 by 8.5 by 4.5 cm. and weighed 210 Gm. The diaphragmatic surface was coated with a thin layer of fibrin. Occasional yellowish-white areas were seen through the capsule. The pulp was grayish red and contained many foci of caseous necrosis ranging from 2 to 12 mm. in diameter (fig. 6). The liver measured 26.5 by 19.5 by 9 cm. and weighed 1,660 Gm. Minute yellow-

ish-white circular foci were seen through the capsule. Some of these were elevated above the surface. Similar nodules, from 1 to 3 mm. in diameter, were sparsely scattered throughout the parenchyma. The cortex of the left adrenal gland contained two small yellowish-white circular foci of necrosis. The lymph nodes in the region of the epiploic foramen and the pancreatic, mesenteric, para-aortic and right iliac lymph nodes were large and edematous, and some contained areas of caseous necrosis. The anatomic diagnosis was caseous pneumonia of the upper half of the upper lobe of the left lung with miliary tubercles in the remaining part of the lung; multiple hemmorhagic infarcts and intrapulmonary thrombosis of the middle and upper lobes of the right lung; bilateral fibrinous pleuritis with serofibrinosanguineous effusion; fibrinous pericarditis with serofibrinosanguineous effu-

Fig. 4.—The upper (greater) half is the inner surface of the pericardium posteriorly, and the lower (lesser) half is the posterior surface of the heart. These surfaces show thick shaggy fibrinous membranes.

sion; multiple foci of caseous necrosis in liver, spleen and left adrenal gland; caseous and suppurative lymphadenopathy of the mediastinal, tracheobronchial, epiploic, gastric, pancreatic, mesenteric, para-aortic and right iliac lymph nodes; ulcerative stomatitis and glossitis; cloudy swelling and fatty changes of the myocardium; Zenker's degeneration of the rectus abdominis muscles; cloudy swelling of the kidneys, and fibrinous perisplenitis. Tularemic pneumonia with pericarditis was considered the cause of death.

Results of Laboratory Tests.—Separate samples of blood and pleural, pericardial and ascitic fluids were removed post mortem. The blood serum and the pleural and pericardial fluids agglutinated Bact. tularense in dilutions up to 1 : 5,120. The

ascitic fluid in a dilution of 1:80 agglutinated the organism. Two rabbits, one inoculated with pleural exudate and the other with pericardial exudate, died a few hours apart on the fourth day, and the typical miliary lesions of tularemia developed in each. A guinea-pig inoculated with ascitic fluid died of peritonitis on the twentieth day. Triturated tissue from the lungs and lymph nodes and treated centrifugated exudates were cultured for Bacillus tuberculosis. The culture mediums remained sterile. Acid-fast stains of smears from caseous material did not reveal any tubercle bacilli.

Microscopic Examination.—The microscopic observations will be described briefly. A detailed report of the pathologic process of tularemia is being planned.

Fig. 5.—The upper lobe of the left lung, showing tularemic pneumonia. Discrete tubercles may be seen in the lower half.

Superficially the ulcers of the tongue (fig. 7) and the mucosa of the left cheek were coated with a thin layer of fibrin, which was mixed with cellular débris. Many polymorphonuclear leukocytes and a few lymphocytes, plasma cells and various monocytes with vacuolated cytoplasm were present immediately beneath the fibrinous layer. The polymorphonuclear cells gradually diminished in number as one approached the deeper portions, so that finally the plasma cells and lymphocytes became the predominating elements. Here, polymorphonuclear cells were scanty. Here, also, because of the lessened cellularity, one could quite definitely distinguish fibrob'asts, histiocytes and endothelial cells. The cytoplasm of the

endothelial cells was vacuolated. No areas of caseous necrosis were present. Necrosis was limited to the superficial portions of the ulcer. A few macrophages were encountered which, when stained with Foshay's method, showed very small coccobacillary micro-organisms. The bacteria stained poorly and could not be shown satisfactorily in photomicrographs. Gram stains revealed a few gram-positive cocci on the surfaces of the ulcers.

The mediastinal and tracheobronchial lymph nodes showed areas of massive caseous necrosis. Almost the entire tissue was composed of caseous granular acellular material which stained with eosin. A thin rim of lymphoid tissue remained between the capsule and the periphery of the caseous masses. Fibroblasts and epithelioid cells were sparingly and rather evenly distributed in the necrotic

Fig. 6.—Largest caseous areas in the spleen.

periphery immediately beneath the rim of lymphocytes. A few of these cells mingled with the lymphocytes. Many of the fibroblasts and epithelioid cells were markedly elongated and arranged parallel to each other and perpendicular to the circumference of the caseous material. The reticulum fibers along the periphery were thickened. They appeared to be increased in amount and disappeared in the caseous material. A few of the nodes of the mediastinum were extensively infiltrated with polymorphonuclear neutrophils, but there was no caseation. The abdominal lymph nodes showed marked destruction of the normal architecture, and various-sized caseous foci were present in all the sections. The peripheries of the caseous areas were much more cellular than those of the thoracic lymph nodes. Occasional giant cells of the Langhans type were encountered. The marked similarity of these lesions to those of caseous tuberculosis prompted an examination

with acid-fat stains. No acid-fast bacilli were found. Minute rods were found in the necrotic areas and epithelioid cells in the sections stained by Foshay's method.

Sections of the large consolidated mass in the lungs showed merely an acellular caseous material in which there were a few aggregations of cellular débris. No vital cells were encountered. Sections from the periphery of the caseated consolidation revealed a confluence of caseous areas (fig. 8). The periphery of the necrotic areas were either acellular or scanty cellular or contained thin rims of densely packed cells. The alveoli between the irregular caseous expansions contained monocytes and a pinkish colloid-like-staining material which was homogeneous, like that present in the lumens of the blood vessels, vacuolated, or vacuolated and granular. This colloid-like material, which undoubtedly was serum, contained no threads of fibrin. The monocytes were large and contained relatively small nuclei and a large amount of clear vacuolated cytoplasm. They were undergoing extensive fatty metamorphosis and showed various stages of degeneration. The cytoplasm of a few of the monocytes contained hemosiderin and

Fig. 7.—Photomicrograph of a section of a tularemic ulcer of the tongue.

anthracotic granules. These monocytes were endothelial leukocytes and desquamated alveolar epithelial cells. The majority appeared to be alveolar epithelial cells. The sequence of the pathologic process was studied from sections taken some distance from the area of caseous consolidation, where small caseous foci were scattered discretely. Apparently, the early reaction consisted of edema of the alveolar wall, swelling of the endothelium of the capillaries, swelling of the alveolar epithelial cells and infiltration of the alveolar wall with lymphocytes and polymorphonuclear leukocytes. Serum without or with a few cells exuded into the alveolar spaces. The alveolar epithelium became swollen and dropped into the serous fluid. Endothelial leukocytes also migrated into the alveolar spaces. Some alveolar spaces were completely filled with closely packed monocytes, whereas others merely contained serous exudate without cells or with few cells. A few other cells, such as lymphocytes, polymorphonuclear neutrophils, plasma cells and eosinophils, were observed in the alveolar spaces; these cells were limited to the alveolar walls and lobular septums and occurred around larger blood vessels and

in the peribronchial connective tissue. In some areas the plasma cells predominated, whereas in other areas the majority of the cells were lymphocytes. The process of necrosis and its usual site of origin were not definitely determined. The necrosis seemed to originate in the alveolar wall or from the serous exudate mixed with mononuclear cells. This problem awaits further study. It was apparent that necrosis did not begin within the blood vessels or around the blood vessels, bronchiolar walls or peribronchial connective tissue. These structures usually suffered destruction when they became incorporated with the advancing necrosis. According to the appearance of the discrete caseous foci, it seemed apparent that in the lung at least the macrophagic response was weak. Very few cellular elements surrounded the periphery of the lesion. There was, however, an attempt to dispose of the deleterious material, and this was evident by the strenuous ameboid efforts of monocytes to penetrate the depths of the necrotic tissue. However, these monocytes apparently were soon destroyed. Some of the monocytic cells were undoubtedly fibroblasts, because they were intimately associated with the few collagenous fibers at the periphery of the caseous areas. Other monocytes resembled epithelioid cells. Poorly formed giant cells of the Langhans type were occasionally encountered at the periphery of a caseous area. The lumens of the small bronchi and bronchioles were filled with necrotic or caseous material. Some of the respiratory tubes, although filled with necrotic material, were perfectly intact and well preserved (fig. 8); others were partially necrotic, and still others were completely necrosed. Thrombosis of the blood vessels was not observed in the left lung. The right lung contained many thrombosed vessels and a few hemorrhagic infarcts; yet this lung was free from tularemic lesions.

There were many small round discrete and large confluent stellate and septate caseous areas in the spleen. Two distinct cellular zones encircled the necrotic, almost acellular material. The inner zone was composed of a scanty, cellular, rather thick layer of ovoid and markedly elongated monocytes mingled with thick strands of collagenous fibers. The strands were definitely continuous with the spindle-form cells. Other monocytes consisted of relatively large, light-staining ovoid nuclei, some of which were indented and recognized as epithelioid cells. A third group of monocytes contained relatively small round or ovoid light-staining nuclei and a large amount of clear cytoplasm undergoing a fatty metamorphosis; these cells were recognized as endothelial cells. The outer zone was cellular and consisted of plasma cells and lymphocytes with a few monocytes and occasional eosinophils. Few polymorphonuclear leukocytes were present in either of the two distinct layers. A few polymorphonuclear leukocytes were found in the caseous material. The peripheries of some of the caseous tubercles occasionally showed hemorrhagic infiltration. Areas of extreme congestion with deposits of abundant hemosiderin were everywhere observed. Giant cells were occasionally encountered.

In the liver the caseous tubercles were all found immediately beneath the capsule (fig. 9). None were observed more than 1 mm. beyond the capsule. They were contiguous with the capsule, or a small layer of liver cells intervened. The caseous foci ranged between 0.5 and 2.5 mm. in diameter and in construction were essentially similar to those of the spleen. Only two giant cells were found in the thirty-five tubercles that were studied. Hemorrhage around the periphery of the tubercles was more frequent in the liver (fig. 9) than in the spleen. Moderate acute hepatitis was present, with rather marked fatty and granular changes of the hepatic cells. The polymorphonuclear infiltration was both central and peripheral, with the intervening liver cells free from leukocytic infiltration. Many of the hepatic cells were filled with bile pigment. The portal areas were infiltrated with

lymphocytes and appeared well preserved. The lumens of several central veins were filled with white thrombi. The parenchyma was congested, and occasionally a small hemorrhage was observed.

The epicardium was coated with a thick layer of acellular fibrin, beneath which a vigorous organization was present. The chief cellular elements in the organizing tissue were lymphocytes, plasma cells and fibroblasts. Numerous capillaries were present. The epicardium was thick, and both the epicardium and the subepicardial tissue were infiltrated with cellular elements similar to those in the organization previously described. The myocardium showed marked granular and fatty changes. No caseous necrosis was observed.

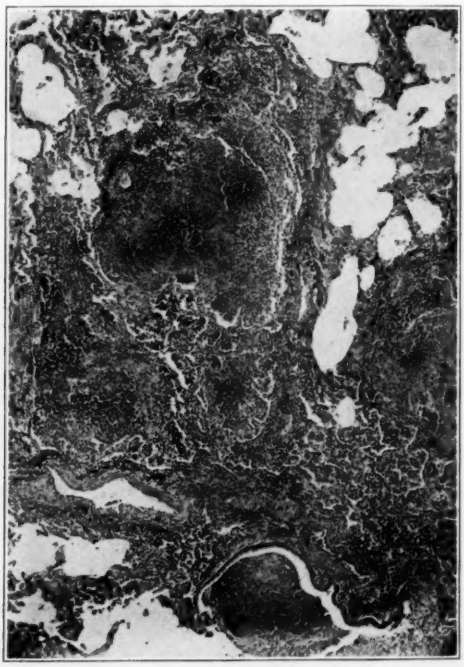

Fig. 8.—Photomicrograph of a section of the lung, showing confluence of caseous foci.

The cortex of the left adrenal gland contained three discrete areas of caseous necrosis, similar in structure to those seen in the liver.

The right rectus muscle showed Zenker's degeneration. There was a marked cloudy swelling of the tubular epithelial cells of the renal cortex. Many sections of kidney tissue were studied, but no foci of caseous necrosis were seen. Bact. tularense was found in the lesions of the lung, spleen, lymph nodes and epicardium. It could not be demonstrated in the liver.

REVIEW OF CASES IN WHICH NECROPSY WAS PERFORMED

It is rather a curious incident that the postmortem examination in each of the 21 cases thus far recorded in the literature was performed by a different person.

Infection occurred in 17 cases from the handling of rabbits, in 2 cases from the bites of deer flies, in 1 case from contact with an opossum and in 1 case from ingestion of the flesh of a rabbit. The usual period of incubation was from three to four days. A period

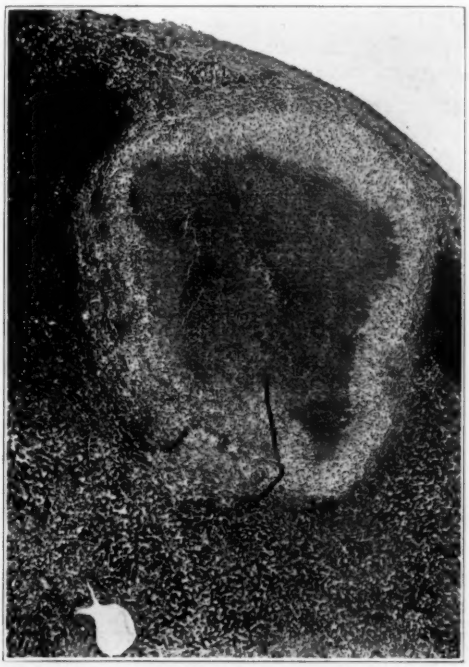

Fig. 9.—Photomicrograph of a subcapsular caseous area of the liver. Hemorrhage is seen at the periphery of the lesion.

of incubation of less than one day was reported by Permar and Maclachlan.[12] Their patient, a Negro, became nauseated and fatigued on the evening of the same day on which he cleaned a large number of rabbits, and on the following day he had chills and fever. The patient of Bardon and Berdez [13] became acutely ill the day after cutting up

12. Permar, H. H., and Maclachlan, W. W. G.: Tularemic Pneumonia, Ann. Int. Med. **5**:687, 1931.

13. Bardon, R., and Berdez, G.: Tularemia: Report of a Fatal Case with Postmortem Observations, J. A. M. A. **90**:1369 (April 28) 1928.

the carcass of a rabbit. The longest period of incubation (seven days) was encountered in Simpson's [2] case. In 18 cases the condition was of the ulceroglandular type, and in 3 cases, of a typhoid character. According to Beck and Merkel,[11] their case is the only one of the typical typhoid type in which necropsy was performed. Permar and Maclachlan's case was probably an instance of the typhoid type, and in our case the condition was of typhoid character during the first thirty-six days of the sixty-four days of illness. The temperature was usually between 101 and 103 F., but occasionally it rose to 105 F. The leukocyte count varied considerably. In 5 cases it was below 8,000. The lowest leukocyte count, 3,300, was reported by Haizlip and O'Neil, and the highest, 22,600, by Goodpasture and House.[14] Eighteen counts were recorded in our case; the lowest was 11,450 and the highest, 18,100. There was always a marked shift to the left, and the band forms in every differential count exceeded the number of segmented neutrophils. Gundry and Warner give the average of 10,800 for 12 cases. The agglutination tests were positive during the second week and were constantly negative before the eighth or the ninth day. Those that performed agglutination tests more than once found that the titer increased during the course of the disease. The titers in Massee's [15] case were 1:40 on the fifteenth day and 1:320 on the eighteenth day; in Hartman's [16] case, 1:640 and 1:1,280 on the fifteenth and eighteenth days, respectively; in Blackford's [17] case, 1:40 on the ninth day and 1:5,120 on the twenty-fifth day; and in Gudger's [9] case, 1:320 on the sixteenth day and 1:5,600 at the end of the third week. The results of agglutination tests in our case were as follows: nineteenth day, negative; twenty-first day, suspicious; twenty-third day, a titer of 1:320; postmortem blood and serous exudates on sixty-fourth day, a titer of 1:5,120. Septicemia and pulmonary involvement predominated clinically. Bronchopneumonia was diagnosed in 7 cases, lobar pneumonia in 4, abscess of the lung in 1 and pleural effusion in 2. Other frequent clinical manifestations were nausea and vomiting, abdominal distention and cough (with or without rusty or blood-streaked sputum). Diarrhea was recorded in 4 cases, and in our case it persisted for ten days.

14. Goodpasture, E. W., and House, S. J.: The Pathologic Anatomy of Tularemia in Man, Am. J. Path. **4**:213, 1928.

15. Massee, J. C.: Tularemia in Georgia: Report of a Case, J. M. A. Georgia **20**:66, 1931.

16. Hartman, F. W.: Tularemic Encephalitis, Am. J. Path. **8**:57, 1932.

17. Blackford, S. D.: Pulmonary Lesions in Human Tularemia: Pathologic Review and Report of a Fatal Case, Ann. Int. Med. **5**:1421, 1932.

Jaundice occurred twice, in Verbrycke's [18] case and in ours. Marked pericardial friction sounds were present in our case. Death usually occurred within from fourteen to twenty days after the onset of the illness; however, Simpson's patient lived only four days and Palmer and Hansmann's eight days. On the other hand, death occurred much later in 3 cases: forty-one days (Blackford), sixty-four days (our case) and five months (Bruecken, cited by Francis and Callender [7]). Bruecken's patient died of septicemia due to Streptococcus haemolyticus and perhaps should not be included in the prognostic summary.

The primary lesion persisted and was found at necropsy in all but 3 cases. Palpable lymphadenopathy was absent in Permar and Maclachlan's case and in ours; however, visceral lymphadenopathy was present in all the cases. Pulmonary lesions were constantly found post mortem. The pathologic changes in the lungs varied; they were described as bronchopneumonia, confluent lobular pneumonia and lobar pneumonia, with or without necrosis or caseation, miliary focal necrosis, abscesses and cavitation and fibrinous pleuritis. Marked pneumonia was present in 10 cases, pleural effusion in 4 and abscess of the lung and cavitation in 2. Areas of necrosis of caseation in the lungs were described in 16 cases. Multiple foci of caseous necrosis were present in the liver 15 times and in the spleen 16 times. Although foci of caseous necrosis are usually present both in the liver and in the spleen, in 3 cases (Francis and Callender, Bunker and Smith [19] and Haizlip and O'Neil) they were absent in the liver and present in the spleen, whereas in 2 other cases (Massee and Permar and Maclachlan) they were present in the liver and absent in the spleen. It is interesting to note that in Simpson's case, in which death occurred four days after the onset, there were multiple caseous foci in the liver and spleen and that in Bruecken's case, in which death occurred about five months after the onset of tularemia, there were also multiple caseous areas in the same organs. Death occurred forty-one days after the onset of the illness in Blackford's case, but no lesions were present in the liver and spleen, whereas in our case, in which the patient died sixty-four days after the onset, many caseous foci were present in those organs. Gudger's patient died thirty-one days after the onset, and no lesions were found in the liver and spleen.

The most common sites of tularemic lesions are therefore the skin, lymph nodes, lungs, liver and spleen. Other tissues and organs are

18. Verbrycke, J. R., Jr.: Tularemia, with Report of a Fatal Case Simulating Cholangeitis, with Postmortem Report, J. A. M. A. **82**:1577 (May 17) 1924.

19. Bunker, C. W. O., and Smith, E. E.: Tularemia: Report of Four Cases, One Fatal, with Autopsy Report, U. S. Nav. M. Bull. **26**:901, 1928.

rarely affected. Foulger, Glazer and Foshay,[20] Schumacher[21] and Gundry and Warner found lesions on the peritoneum. Hartman[16] and Bryant and Hirsch[22] have convincingly demonstrated lesions in the meninges and brain. The adrenal glands in a case of Francis and Callender contained multiple necrotic foci. Two caseous foci were noted grossly and three microscopically in the left adrenal gland in our case. The kidneys undoubtedly possess a striking resistance against tularemic infection, even in the experimental animals; yet Bardon and Berdez found a few nodules, similar to those of the spleen, in the kidneys of their patient. In the unusual and interesting case of Beck and Merkel, ulcers were present in the stomach, duodenum, ileum and cecum. Tularemic fibrinous and caseous pericarditis and tularemic ulcerative stomatitis with ulcerative glossitis were present in our case.

COMMENT

Tularemia can be readily diagnosed when one is confronted with the usual classic history and objective findings. However, when the history is vague and recondite and when external lesions are absent, one must conclude that "the most important fact in the diagnosis of tularemia is to have the disease in mind."[23] The unusual and perplexing cases are hailed as the typhoid and pneumonic forms of tularemia. We have been strongly influenced by the observations of the ulceroglandular, oculoglandular and glandular types but rather inattentive to the less frequent forms. Undoubtedly a surprising number of unusual cases of tularemia have escaped correct diagnosis both by the clinician and by the pathologist. Some of the most interesting cases would have eluded recognition if it had not been for the alert clinicians' demands for agglutination tests. These cases would also have escaped recognition at postmortem examination because the gross pathologic picture and, according to some investigators, the microscopic pathologic picture are similar to those seen in cases of tuberculosis. A few have even insinuated that at necropsy in fatal cases of tularemia the condition has been diagnosed as pulmonary tuberculosis or miliary tuberculosis. On the other hand, as in our case, it is definitely known that internists,

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20. Foulger, M.; Glazer, A. M., and Foshay, L.: Tularemia: Report of a Case with Postmortem Observations and a Note on the Staining of Bacterium Tularense in Tissue Section, J. A. M. A. **98**:951 (March 19) 1932.

21. Schumacher, H. W., cited by Francis, E.: Symptoms, Diagnosis and Pathology of Tularemia, J. A. M. A. **91**:1155 (Oct. 20) 1928.

22. Bryant, A. R., and Hirsch, E. F.: Tularemic Leptomeningitis: Report of a Case, Arch. Path. **12**:917 (Dec.) 1931; Tr. Chicago Path. Soc. **14**:9 (June 1) 1932.

23. Simpson, W. M.: Tularemia: Summary of Recent Researches, Ohio State M. J. **29**:35, 1933.

surgeons and dermatologists have erroneously diagnosed the condition in the fatal cases as influenza, chronic bronchitis, typhoid, septicemia, tuberculosis, an acute abdominal condition, acute cholecystitis, cholelithiasis, cholangeitis, pyelitis, peritonitis, syphilis, pustular acne and sporotrichosis. Even the serologist, because of the cross-agglutination of Bact. tularense with Br. abortus and Br. melitensis, caused tularemia to be diagnosed as undulant fever. The blood serum of the patients of Gudger and of Beck and Merkel agglutinated B. paratyphosus. Verbrycke's patient, because of jaundice and acute abdominal symptoms, underwent an unnecessary exploratory laparotomy.

Verbrycke's case, the first in which necropsy was reported, is an excellent illustration revealing the importance of an accurate history. The patient and her relatives misunderstood the physician's questions, and the result was that the correct information was not obtained until after the patient died. However, it is not infrequently encountered that the physician is faulty in taking the history. It must be kept in mind that rabbits, flies and ticks, while they are the most frequent source of infection, are not the only purveyors of tularemia. The squirrel, wild rat and mouse, woodchuck, hog, coyote, cat, opossum, grouse and quail have infected man. The guinea-pig has been the source of infection among laboratory workers. The following insects are known to convey the bacillus: rabbit louse, mouse louse, squirrel flea, bedbug and stable fly. Man to man infection has not been observed.

It has been conclusively proved that the portal of entry is not always a wound in the skin. The pioneer workers, Francis, Mayne and Lake, had tularemia without evidence of portal of entry.[24] Simpson has demonstrated that the organism will penetrate the unbroken skin of the guinea-pig. Cases of tularemia without demonstrable lesions have been reported by Francis. The heroic subject Madam Ohara enabled her husband [25] to prove that Bact. tularense can penetrate the unbroken skin. She contracted tularemia after Ohara rubbed the myocardium and blood of an infected rabbit on the hairy part of her hand and thumb. That the ingestion of insufficiently cooked rabbit meat produced the disease in seven members of a Negro family was reported by Crawford.[26] Many of Ohara's patients stated that they were poisoned by eating the flesh of rabbits. Permar and Maclachlan suggested the possibility of primary

24. Simpson, W. M.: Tularemia: History, Pathology, Diagnosis and Treatment, New York, Paul B. Hoeber, Inc., 1929.

25. Ohara, Hachiro: Experimental Inoculation of Disease of Wild Rabbits into the Human Body, Japan M. World **6**:300, 1926.

26. Crawford, M.: Tularemia from the Ingestion of Insufficiently Cooked Rabbit, J. A. M. A. **99**:1497 (Oct. 29) 1932.

infection of the respiratory tract in tularemic pneumonia. It is thus apparent that the unbroken skin and the alimentary and the respiratory tract may be the primary portal of entry.

The various clinical manifestations and necropsy observations indicate that the cause of death varies. Foshay [27] has collected reports of a series of fatal cases, and in a forthcoming paper he intends to elucidate the cause and mode of death and the possibility of preventing death with serum therapy. He has assembled the fatal cases into four groups:

Group 1. In this group primary bacteremia is followed by fatal septicemia, death occurring within ten days. The patients lack a natural resistance and react as rodents.

Group 2. This group consists of cases of "tularemic sepsis." Death occurs during the third or fourth week of sickness; the average length of time before death is eighteen days. Primary bacteremia disappears, but secondary bacteremia develops owing to necrosis of blood vessels in caseous foci, as in tuberculosis. Another possible cause for the development of this secondary bacteremia may be the lymphogenous transportation of bacteria into the blood stream after the material drained from infected tissues has emptied into the cisterna chyli, the thoracic duct or the right lymphatic duct. Most of the fatal cases occur in this group.

Group 3. In the cases in this group tularemic pneumonia predominates clinically, and death is due to intoxication.

Group 4. In the cases in this group death occurs six weeks or more after a collapse of the immune mechanism or as a result of previous pathologic processes in various organs.

The cases of Simpson and Palmer and Hansmann belong to group 1. According to Foshay, "tularemic sepsis" (group 2) is treacherous and clinically may occur with the mildest infections. Foshay expressed the belief that 1 of every 15 patients will have "tularemic sepsis." He stated that there is no way of predicting its arrival, and that in cases of mild infection it is a dramatic change. Once sepsis has occurred, the patient rarely survives for more than six or seven days.

The duration of the disease is usually comparatively short, and the majority of persons recover. However, the period of convalescence is of comparatively long duration. In a few cases the condition runs a chronic course. Nakada's [28] patient remained in the hospital for seven and one-half months. The duration of the disease and convalescence

27. Foshay, Lee: Personal communication to the author.
28. Nakada, J. R.: Tularemia (Three Cases), J. Missouri M. A. **30**:120, 1933.

can be considerably shortened and the prognosis rendered entirely favorable by treating the patient with Foshay's antiserum. According to Foshay,[27] not a single fatality occurred in 350 patients treated with antiserum. On the basis of the mortality rate, there should have been 22 deaths in Foshay's group if serum therapy had been omitted. Simpson [29] emphasized the fact that Foshay's antiserum produced a prompt and favorable influence on the fever and lymphadenopathy and stated that when the results in a series of cases in which treatment is administered are compared with those in cases in which no treatment is given, there is "little doubt as to the efficacy and specificity of the treatment."

Since agglutination tests in cases of tularemia are not positive until the second week and in not a few instance until after the second week (twenty-third day in our case), a more rapid diagnostic method should meet with approval. Foshay's skin test (the injection of bacteria killed with formaldehyde and subsequently treated either with a solution of hydrogen peroxide or with nascent nitrous oxide) has proved to be a reliable diagnostic procedure.

The gross pathologic picture in fatal cases is rather characteristic, particularly when multiple small necrotic foci are present in the lungs, liver and kidneys. These lesions may be confused with those seen in miliary tuberculosis.

The histopathologic picture of tularemia will probably be placed in the category of specific inflammations in the near future. At present, the microscopic observations are meager and contradictory. Necrosis in tularemia has been attributed to vascular occlusion. Simpson maintained that vascular occlusion due to thrombosis does not cause caseation. I firmly believe that thrombosis and vascular occlusion result from the spread of necrotization. Patent lumens with fairly well preserved vascular walls in the midst of caseous areas were observed in our case.

SUMMARY

The clinical and necropsy studies in a case of tularemic pneumonia with pericarditis and ulcerative stomatitis are presented.

The importance of publishing the results of necropsy in all cases of tularemia is emphasized.

All published reports on necropsies (21 to date) in fatal cases of tularemia are reviewed.

The mode of infection, the clinical course and the diagnostic and therapeutic procedures are discussed.

29. Simpson, W. M.: Personal communication to the author.

ADDENDUM

For some inexplicable reason I failed to include Kavanaugh's [30] case in the review of all reported cases of tularemia in which necropsy was performed. Kavanaugh's patient had primary ophthalmic tularemia. Death occurred twelve days after the onset. Necropsy revealed fibrinopurulent membranous palpebral conjunctivitis of the right eye; preauricular, superior cervical, submaxillary, mediastinal, hilar, mesenteric and retroperitoneal lymphadenopathy; multiple foci of necrosis in the lungs, liver and spleen, and fibrinopurulent peritonitis. Complete clinical information on this case was not presented, but from the various sections of the paper it was gathered that infection occurred after dressing a wild rabbit and that clinical symptoms of pulmonary involvement and general peritonitis were present. Thus necropsy has been reported in *22* cases of tularemia in this country to date (July 18, 1935).

30. Kavanaugh, C. H.: Tularemia, Arch. Int. Med. **55**:61 (Jan.) 1935.

LYMPHEDEMA (ELEPHANTIASIS) OF THE EXTREMITIES CAUSED BY INVASION OF LYMPHATIC VESSELS BY CANCER CELLS

REPORT OF TWO CASES

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In the two unusual cases reported here, lymphedema (elephantiasis) of the extremities was the result of malignant invasion of the lymphatic structures. In the first case the condition was caused by a squamous cell epithelioma extending from the left ankle to the groin, and in the second case the cause probably was direct extension of an endothelioma of the pleura to the lymphatic structures of one arm. Lymphedema, or elephantiasis (an advanced stage of lymphedema), of the extremities rather frequently results from metastatic involvement of inguinal or axillary lymph nodes or from surgical removal of lymph nodes, especially those which are involved in cases of carcinoma of the breast. Development of lymphedema as the result of packing of the lymphatic channels of an extremity with tumor cells, thus obstructing the flow, is, I believe, uncommon. The various types of lymphedema of the extremities and their relative frequency of occurrence recently have been reviewed by Allen.[1]

REPORT OF CASES

A farmer aged 56 years was seen in the Mayo Clinic in June 1934, because of swelling of the left leg. Eight years previously a small nodule had appeared on the medial aspect of the left ankle, and shortly thereafter a mass had appeared in the left groin. A physician of the patient's home community had excised from the left ankle a lesion the size of a quarter-dollar (about 2.5 cm. in diameter), and from the groin the same physician had removed a large nodule. On the basis of examination of the tissue, a diagnosis had been made of sarcoma of the ankle and of an inflammatory reaction in the left groin. Edema of the ankle gradually had developed and had proceeded up the leg. The patient had received thirteen roentgen treatments without any evidence of improvement. Generalized edema of the leg had been present for four years, but this had not progressed during the year previous to the patient's visit to the clinic. In the course of the four years mentioned, the patient had had four attacks of recurrent lymphangitis and cellulitis associated with chills, fever and nausea and vomiting. Treatment had consisted of local application of heat and ointments to relieve the swelling of the leg. Roent-

From the Section on Dermatology and Syphilology, The Mayo Clinic.

1. Allen, E. V.: Lymphedema of the Extremities: Classification, Etiology and Differential Diagnosis; a Study of Three Hundred Cases, Arch. Int. Med. **54**:606 (Oct.) 1934.

gen treatment had not been given for five years before the man came to the clinic. He had not lost weight.

Examination revealed an indolent ulcer of the left ankle and marked lymphedema (elephantiasis) of the left leg. In many areas the skin had a verrucous appearance, such as frequently is seen in cases of benign lymphedema (fig. 1). The ulcer was indurated, but it lacked a pearly border. Characteristics of squamous cell epithelioma, sarcoma and endothelioma were considered in making the diagnosis. There was no evidence of varicose veins. Extending up the leg were many discrete hard subcutaneous nodules, which apparently followed the course of

Fig. 1 (case 1).—Squamous cell epithelioma of the ankle, with resulting elephantiasis.

the lymphatic structures. There was no evidence of arsenical pigmentation or of keratosis. There was a large, hard mass, about 12 cm. in diameter, in the left iliac fossa. General examination, including roentgenograms of the pelvis and the leg for evidence of involvement of bone, gave essentially negative results. Excision of the inguinal mass revealed a great cluster of lymph nodes, which were fairly soft. Examination of a specimen taken for biopsy disclosed squamous cell epithelioma of grade 2. Involvement of the iliac fossa was too extensive to warrant surgical intervention. Palliative treatment with roentgen rays seemed contraindicated because of the possible danger of increasing the degree of elephantiasis.

Comment.—This case is of interest from several points of view. An original diagnosis was made of sarcoma of the ankle. In view of the data, however, I am certain that the original lesion was an epithelioma rather than that there was a change from sarcoma in the primary lesion to epithelioma in the metastatic growths which were found in the lymph nodes. I have observed several cases of neoplasm of the extremities in which the histologic picture at first glance suggested sarcoma or even endothelioma but in which, through serial section, it was possible to demonstrate the origin of the tumor cells from the epidermis and in small areas typical prickle cells of a squamous cell epithelioma could be found.

Despite the absence of loss of weight, the malignant character of the ulcer in this case seemed definite. Cases have been reported, however, in which malignant growth was thought to be present but on histologic examination of tissue the condition was found to have resulted from tuberculosis or varicose ulcer. The latter, of course, also may rarely eventuate in epithelioma. The four attacks of recurrent lymphangitis and cellulitis in my case might have suggested an inflammatory basis for the elephantiasis. That lymphangitis and cellulitis may be expected as secondary and contributing factors to elephantiasis is readily understood on the basis, first, of infection of the open ulcer and, second, of the inflammatory reactions associated with epithelioma. Whether roentgen treatment had anything to do with the subsequent increase in elephantiasis is difficult to decide.

In most cases of epithelioma of the extremities elephantiasis, or lymphedema, does not develop. Beck [2] barely referred to elephantiasis associated with epithelioma in these regions. Cesareo de Asis,[3] in a review of a large series of cases of carcinoma (epithelioma) of the lower extremities, did not mention elephantiasis. Conversely, Muller and Jordan,[4] in a review of elephantiasis nostra, did not mention epithelioma as an etiologic factor, nor is this mentioned in recent textbooks on dermatology as a possible cause of elephantiasis. In a recent study [5]

2. Beck, S. C.: Geschwülste der Haut (II): Epithelioma, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12, p. 208.

3. de Asis, Cesareo: Cutaneous Carcinoma of the Lower Extremities: A Study of Cases at the Barnes and Barnard Free Skin and Cancer Hospital of St. Louis, Missouri, Ann. Surg. **83**:663 (May) 1926.

4. Muller, G. P., and Jordan, C. G.: Elephantiasis Nostra, Ann. Surg. **97**: 226 (Feb.) 1933.

5. Montgomery, Hamilton: Arsenic as an Etiologic Agent in Certain Types of Epithelioma: Differential Diagnosis from, and Further Studies Regarding, Superficial Epitheliomatosis and Bowen's Disease, Arch. Dermat. & Syph. **32**:218 (Aug.) 1935.

of epithelioma, whether the sequel of arsenical keratosis of the palms and soles or independent thereof, none of the patients had associated elephantiasis, nor did I find mention of such an association of conditions in the literature on the subject which I reviewed. Allen [6] found that in 10 per cent of three hundred cases of lymphedema the condition was attributable to malignant occlusion of the lymphatic channels, but in the majority of these cases carcinoma of the breast was an associated condition. In only three cases (1 per cent) did the elephantiasis result from an epithelioma, or a melano-epithelioma, of an extremity, and in each of the three cases the lymphedema developed only after surgical removal of lymph nodes from the groin. Judging from recent articles, the percentage of elephantiasis that is attributable to epithelioma of an extremity is small, but epithelioma always should be considered as a possible etiologic agent.[7]

CASE 2.—A basket-weaver aged 52 was seen in the clinic in November 1927, because of swelling of the right arm of six months' duration. Three years previously he had noted a neuritic pain in the right shoulder, which lasted a year before it disappeared. Simultaneously with the swelling of the arm, a red area appeared in the right pectoral region and spread over the abdomen, the flank, the remainder of the thorax and the arm. A history of attacks of erysipelas or cellulitis was not obtained.

Examination revealed definite edema of the whole right arm, which was about one and one-half times the size of the left arm. The right side of the trunk was similarly edematous. In the axilla the skin had a verrucous appearance. The axillary lymph nodes were slightly enlarged. In places, there were thick-walled, vesicle-like elevations, from which, when they were opened, there exuded a watery secretion. Roentgenograms of the thorax gave evidence of rather marked fibrosis. The roentgenologist, who did not know the patient's occupation, asked if he was a miner, because of the type of pulmonary changes. Neurologic examination gave negative results. It was thought that the obstruction of the lymphatic flow came from within and might be the result of obstruction of the right thoracic duct. The differential diagnosis also included the possibility of the presence of tuberculous lymph nodes, with secondary obstruction, hypertrophic lymphangioma and scleroderma. A malignant process was not seriously considered. There was no evidence of a cervical rib.

A specimen for biopsy was taken from about the level of the iliac crests and another from the right flank; a most unusual histologic picture was revealed (fig. 2). All the lymph vessels were packed with large mononuclear cells in which were many mitotic figures, and evidence was present also of amitotic cell division. In other cells pyknosis of the nuclei and degenerative changes in the cytoplasm were noted. A few of the tumor cells were seen between connective tissue bundles, but evidence of a malignant lymphangio-endothelioma of the skin, such as has been described by Nather,[8] was not observed. The cells were not sufficiently differ-

6. Allen, E. V.: Personal communication to the author.

7. Nobl: Kombinierte Erscheinungsform eines Fersencarcinoms mit tuberöser Elephantiasis, Zentralbl. f. Haut- u. Geschlechtskr. **11**:464, 1924.

8. Nather, Karl: Ueber ein malignes Lymphangioendotheliom der Haut des Fuses, Virchows Arch. f. path. Anat. **231**:540, 1921.

entiated to justify certainty as to whether they were endothelial or whether they were metastatic cells from adenocarcinoma. The consensus of the pathologists who examined the sections was that the cells simulated most closely those seen in cases of endothelioma of the pleura, and it seemed most likely, therefore, that tumor cells from a cancer of the lung had worked into the lymphatic channels of the arm, causing obstruction and resultant elephantiasis.

The patient did not stay at the clinic for treatment. He returned home, and some high voltage roentgen therapy was administered. Five months later a physician from the patient's town wrote that he had lost about 30 pounds (13.6 Kg.) and was short of breath on exertion, although the roentgen treatment had helped to reduce the edema of the arm. It has been impossible to follow the patient further.

Fig. 2 (case 2).—Section of a metastatic endothelioma. The lymphatic channels are packed with tumor cells; × 68.

Comment.—This patient's condition is an example of lymphedema and early elephantiasis of the right arm, thorax, back and flank, the result probably of direct extension of a so-called endothelioma of the pleura. The small size of the axillary nodes tended to preclude their being factors in the lymphedema of the arm and would justify the presumption that the lymphatic structures of the arm, as well as those at the level of the iliac crests and those of the right flank, were packed with tumor cells. Although vesicle-like elevations of the skin were present, histopathologic studies did not permit classification of the case as an instance of one of the various forms of lymphangioma, lymphangioblastoma, endothelioma or lymphangio-endothelioma of the skin

(Gans [9]). The rapid loss of weight five months after the patient had left the clinic would support the diagnosis of an internal malignant process, with metastasis to the lymphatic structures of the skin. However, in the absence of a report of postmortem examination, it can only be assumed that the diagnosis of endothelioma of the pleura, with metastasis, was correct. There was no abrasion of the skin or histologic evidence of a lesion of epitheliomatous origin.

In the literature are reports of cases of bilateral, as well as of unilateral, involvement of the extremities, the result of metastasis to the axillary and inguinal nodes from carcinoma of the internal organs. The most important point, however, is that clinically the lymphedema (mild elephantiasis) of the arm and right side of the trunk did not suggest that a malignant process was present, and that one was present was confirmed only by histopathologic study of a specimen taken for biopsy.

9. Gans, Oscar: Histologie der Hautkrankheiten: Die Gewebsveränderungen in der kranken Haut unter Berücksichtigung ihrer Entstehung und ihres Ablaufs, Berlin, Julius Springer, 1928, vol. 2, p. 413.

EVALUATION OF MEASURES OF RENAL FUNCTION IN PERSONS WITH ARTERIOSCLEROTIC BRIGHT'S DISEASE

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Although disease of the renal arterioles is the most constant morphologic expression of essential hypertension, derangement of renal function leading to death from uremia occurs in only a small number of patients with this disease. However, the attention of physicians has been so focused on the possibility of this dread outcome for persons with hypertension that they are accustomed to undertake a careful study of the renal function of their patients in the hope of assuring them that uremia is remote. It becomes pertinent to inquire into the merits of the various tests proposed for measuring renal function in the hope of selecting those which are simple and inexpensive in execution and delicate in response. The latter, more important, requirement is in part a matter of interpretation. It will depend on a strict definition of the degree of variation in result when the test is performed on normal persons. When contrasted with the result obtained in a group of persons who have a pathologic alteration of the renal parenchyma, the test giving the most consistent and pronounced variation from the norm is presumably the most delicate. This is subject to the important condition that no disturbing extraneous factor is present in either group.

We here present a study of the results given by several tests of renal function as applied to a group of 111 patients with essential hypertension. In applying the aforementioned criteria as a measure of the delicacy of the tests used, a disturbing factor of importance was encountered. It will be shown that, aside from the question of actual decrease in kidney substance, impairment of cardiac function influences the result of at least one of the tests so as to make the interpretation of correlations both difficult and obscure.

MATERIAL AND METHODS

Hospitalized private patients were selected on the basis of a systolic blood pressure exceeding 150 mm. of mercury in the absence of evidence of hemorrhagic Bright's disease or other disease accompanied by elevated blood pressure (coarctation of the aorta, hyperthyroidism, etc.). There were 42 men and 69 women

From the Laboratories of the Cottage Hospital.

varying in age from 22 to 80 years, with an average of 59.1 years. None of the patients had congestive heart failure, acute infection or severe metabolic disturbances. They were fed the regular hospital diet, with no restriction of the amount of sodium chloride. Studies of renal function were not instituted until the patient had been in the hospital for several days.

The following tests were studied:

1. The excretion [1] of phenolsulfonphthalein was determined in 111 instances. The phenolsulfonphthalein, accurately measured in a tuberculin syringe, was given intravenously after the emptying of the bladder and the consumption of 400 cc. of water. The results were reported in terms of two hour total excretion.

2. The urea clearance was studied in 33 instances. The recommended technic [2] was rigidly adhered to. Four hundred cubic centimeters of water was ingested at the beginning of the test in the hope of securing a maximum clearance, but frequently the rate of formation of urine did not reach 2 cc. per minute. The values obtained for clearance for the first and second hour were averaged. The results were expressed in terms of the percentage of normal.[3]

3. The creatinine test of Major [4] was carried out in 34 instances, by the original technic. The results were calculated in terms of milligrams of creatinine per hundred cubic centimeters of urine.

4. The dilution and concentration test of Volhard [5] was also studied. The technic adopted was as follows: At 8 a. m., after the emptying of the bladder, 1,000 cc. of water flavored with fruit juice was quickly consumed. Specimens of urine were collected at two hour intervals thereafter until 8 p. m., and a single specimen was collected for the twelve hour period from 8 p. m. to 8 a. m. A dry breakfast was served at 8:30 a. m., and no fluid was consumed until the evening meal. Later in the study, a dry diet was instituted for the entire twenty-four hour period following the initial ingestion of fluid. Thirst was not ordinarily complained of. The volume of urine was measured to within ± 5 cc. and the specific gravity to within ± 0.002 by standardized hydrometers, with a correction for changes in temperature when indicated. Correction for albumin [6] was not necessary in this study.

Choice of Normal Standards.—It is regrettable that the normal response for these tests as defined by numerous investigators has not ordinarily been expressed with a statistical statement as to normal variation. For purposes of comparison, we adopted somewhat arbitrarily the following lowest limits of normal: a phenolsulfonphthalein excretion of 55 per cent in two hours, a urea clearance of 60 per cent of normal, and a creatinine excretion in which the concentration for the second

1. Rowntree, L. G., and Geraghty, J. T.: An Experimental and Clinical Study of the Functional Activity of the Kidneys by Means of Phenolsulphonphthalein, J. Pharmacol. & Exper. Therap. **1**:579, 1910.

2. Möller, E.; McIntosh, J. F., and Van Slyke, D. D.: Studies of Urea Excretion: II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, J. Clin. Investigation **6**:427 (Dec.) 1928.

3. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Methods, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 566.

4. Major, H. M.: The Creatinine Test for Renal Function, Arch. Int. Med. **33**:89 (Jan.) 1924.

5. Volhard, F., and Suter, F.: Nieren und ableitende Harnwege, Berlin, Julius Springer, 1931, p. 165.

6. Lashmet, F. H., and Newburgh, L. H.: The Specific Gravity of the Urine as a Test of Kidney Function, J. A. M. A. **94**:1883 (June 14) 1930.

hour is at least twice that of the first while that of the third hour well exceeds that of the first. The normal response to the test for dilution and concentration was given by Volhard [7] and others [8] as a swing in specific gravity from about 1.001 to 1.029 and the excretion of a volume of urine within four hours equal to the amount of fluid ingested.

TABLE 1.—*Definitions of Diuretic, Diluting and Concentrating Ability and of Nocturnal Polyuria*

Diuretic ability

Conditions: Urine formed over a four hour period of rest in bed after the ingestion of 1,000 cc. of water

Odds that a normal person will secrete as small or a smaller volume than those given:

Cc.	Odds
648	1 in 2
448 or less	1 in 6
348 or less	1 in 12
248 or less	1 in 28
148 or less	1 in 88
48 or less	1 in 400

Diluting ability

Conditions: Urine collected two hours after the ingestion of 1,000 cc. of water

Odds that a normal person will elaborate urine having as high or a higher specific gravity than those given:

Specific Gravity	Odds
1.009	1 in 2
1.012 or more	1 in 6
1.015 or more	1 in 22
1.018 or more	1 in 186
1.021 or more	1 in 2,984

Concentrating ability

Conditions: Abstention from fluids up to 7 p. m.

Odds that a normal person will elaborate urine having as low or a lower specific gravity than those given:

Specific Gravity	Odds
1.027	1 in 2
1.023 or less	1 in 8
1.019 or less	1 in 44
1.015 or less	1 in 740
1.011 or less	1 in 3,174

Nocturnal polyuria

Conditions: Abstention from fluids for twenty-four hours after the ingestion of 1,000 cc. of water

Odds that a normal person will secrete as large or a larger twelve hour volume of urine than those given:

Cc.	Odds
236	1 in 2
406 or more	1 in 6
476 or more	1 in 44
546 or more	1 in 740
616 or more	1 in 31,746

In an attempt at simplification, our technic varied from that of Volhard. We used 1,000 cc. of fluid instead of 1,500 cc. as recommended by him, and we collected our specimens of urine every two hours instead of every half-hour. It became necessary to establish the limits of normal response under these modified

7. Volhard and Suter,[5] p. 166.

8. Munk, Fritz: Pathologie und Klinik der Nierenerkrankungen, Berlin, Urban & Schwarzenberg, 1925, p. 92. Lebermann, F.: Der Wasserversuch als Nierenfunktionssprüfung, Dresden, Theodor Steinkopff, 1932.

conditions. The test was conducted on a group of 25 normal persons having a sex and age distribution similar to that of the patients with hypertension. In addition, the effect of allowing or withholding breakfast on the volume and specific gravity of the urine collected over a four hour period after the ingestion of water was studied in a group of 12 nurses. It was found that the volume of urine was not appreciably influenced. The specific gravity of the first two hour specimens when breakfast was withheld averaged 1.007 ± 0.0005. The ingestion of a dry breakfast elevated the average specific gravity to 1.009 ± 0.0004. The patients in this study received breakfast during the test.

Under the conditions imposed by our technic, it was found that in the four hour period undamaged kidneys excreted an average volume of urine of 648 cc., with a standard deviation of ± 213 cc. The specific gravity of the first two hour specimens, regarded as a measure of diluting ability, averaged 1.009, with a standard deviation of ± 0.0035. The highest values for specific gravity encountered in specimens collected during the afternoon (concentrating ability) averaged 1.027, with a standard deviation of ± 0.004. The volume of urine excreted at night averaged 236 cc., with a standard deviation of ± 70 cc., and the specimens had an average specific gravity of 1.029, with a standard deviation of ± 0.005.

Statistical definitions, under these conditions, of diuretic, diluting and concentrating ability and of nocturnal polyuria, are expressed in table 1.[9] For purposes of comparison with the other tests, the power of dilution was considered impaired if the lowest specific gravity of a morning specimen was 1.012 or above, while the lowest limit of normal concentration for urine excreted in the afternoon was taken as 1.024.

CORRELATION OF RESULTS

In table 2, the number of low results given by each test are tabulated and compared with each other in terms of percentage agreement. Impaired diluting ability and creatinine excretion were encountered in approximately one quarter and one third, respectively, of the patients on whom these tests were made. Urea clearance, concentration and phenolsulfonphthalein excretion were low in slightly less than one half of the patients in each group. In general, the agreement between the results of the tests was vague and little better statistically than might have been expected as a chance occurrence, i. e., a 50 per cent chance that if one test gave a low result in a person another might do likewise. The only suggestive correlations were that in persons with impaired diluting ability the urea clearance was low in 66.6 per cent and that low urea clearance was accompanied by an impairment of phenolsulfonphthalein excretion in 62.5 per cent of the instances. Approximately one third of each of the groups of persons having faulty diluting and concentrating abilities showed no disturbance of renal function as measured by the remaining tests. A similar discrepancy of results was present in one quarter of each of the groups of patients having a low rate of phenolsulfonphthalein excretion, a low urea clearance and a low creatinine output. This again conforms to the percentage of discrepancy to be expected if the results be due to chance alone.

9. We are indebted to Thomas Addis for this method of presentation.

The urea nitrogen level of the blood was measured in 67 patients whose diluting and concentrating abilities and whose phenolsulfonphthalein excretion were studied. In 18 instances it was 20 mg. per hundred cubic centimeters, or more, distributed as follows: One patient had impaired dilution, concentration and phenolsulfonphthalein excretion; 3 had lowered dilution and phenolsulfonphthalein excretion; 5 had faulty concentration and phenolsulfonphthalein excretion, while 3 had impairment of only one function—dilution, concentration or phenolsulfonphthalein excretion. An increased amount of urea nitrogen in the blood correlated more closely with a lowered phenolsulfonphthalein excretion (12 of the 18 instances) than with the results of the other tests.

Feeling that the lack of correlation between the results of these various tests might be due to our arbitrarily chosen boundaries between

TABLE 2.—*Percentage Agreement Between Abnormal Results as Given by Each Test*

Test	Total Number Done	Number in Which Test Was Low	Dilution Also Low, Percentage	Concentration Also Low, Percentage	Phenolsulfonphthalein Excretion Also Low, Percentage	Urea Clearance Also Low, Percentage	Creatinine Excretion Also Low, Percentage	Reactions to All Tests Normal, Percentage
Dilution	111	28	....	39.3	50.0	66.6	44.4	39.3
Concentration	111	51	21.5	....	52.9	40.0	41.1	31.3
Phenolsulfonphthalein excretion	111	51	27.4	52.9	....	52.6	33.3	23.5
Urea clearance	33	16	12.5	37.5	62.5	....	Not done	25.0
Creatinine excretion	35	12	33.3	58.3	58.3	Not done	....	25.0

the normal and the abnormal, we calculated the average phenolsulfonphthalein excretion at the various levels of specific gravity encountered in the tests of dilution and concentration and at various levels of urea clearance. The results are tabulated in table 3. For purposes of better visualization, the statistical differences, derived from the standard deviations, as regards the expected occurrence of a normal phenolsulfonphthalein excretion at these levels, are expressed in terms of odds. While the average phenolsulfonphthalein excretion, as indicating a trend, was somewhat less when there was obvious impairment of renal function, as measured by the efficiency of dilution and concentration, the variation in individual responses was so great that, to judge from these data, it is hazardous to predict in a given instance whether or not a lowered phenolsulfonphthalein excretion will be accompanied by a deficiency in diluting and concentrating abilities. The same appears to be true as regards the correlation between a low urea clearance and the excretory response to phenolsulfonphthalein, but here the relatively small series of cases leaves room for doubt.

EFFECT OF CARDIAC WEAKNESS ON MEASURES OF RENAL FUNCTION

Functional response of the kidneys is presumably extremely sensitive to changes in circulatory environment. Alteration in the amount and pressure of blood flow through the glomerular tufts or stasis in the venules, if sufficiently pronounced or prolonged, may, particularly if the amount of renal parenchyma is decreased, as it is in the arteriosclerotic kidney, detectably influence the clinical measurements of renal

TABLE 3.—*Average Phenolsulfonphthalein Excretion at Various Levels of Specific Gravity and of Urea Clearance*

Concentration					
Specific gravity.....	1.015 to 1.018	1.019 to 1.022	1.023 to 1.026	1.027 to 1.030	1.031+
Average phenolsulfonphthalein excretion, percentage of normal	47.3 ± 4.6	57.9 ± 3.2	54.5 ± 2.7	57.6 ± 3.1	65.5 ± 6.9
Odds for phenolsulfonphthalein excretion, 55 per cent or over.....	1 in 2	1.1 in 2	1 in 2	1.1 in 2	4 in 5
Dilution					
Specific gravity.....	1.016 to 1.013	1.012 to 1.009	1.008 to 1.005	1.004 to 1.000	
Average phenolsulfonphthalein excretion, percentage of normal	55.2 ± 4.0	51.5 ± 3.1	58.9 ± 2.3	62.6 ± 3.7	
Odds for phenolsulfonphthalein excretion, 55 per cent or over.....	1 in 2	1.1 in 2	1 in 2	4 in 5	
Urea clearance					
Percentage of normal*	35 to 50	55 to 70	75+		
Average phenolsulfonphthalein excretion, percentage of normal	55.5 ± 3.2	44.6 ± 3.9	60.5 ± 6.6		
Odds for phenolsulfonphthalein excretion, 55 per cent or over.....	1 in 2	4 in 5	1.3 in 2		

* Thirty-four tests.

function. In a hypertensive patient, particularly, with his labile circulatory apparatus, variability in blood flow might so disturb the outcome of studies of renal function as to lead to untrustworthy deductions regarding the amount of healthy renal parenchyma and to confusion in results when several measures are applied under various states of circulatory adjustment. That the rate of phenolsulfonphthalein excretion may be depressed in a patient with heart failure is attested by the observations of several workers (Frothingham and Smillie;[10] Hopkins and

10. Frothingham, C., Jr., and Smillie, W. G.: The Relation Between the Phenolsulphonphthalein Excretion in the Urine and the Nonprotein Nitrogen Content of the Blood in Human Cases, Arch. Int. Med. **14**:541 (Oct.) 1914.

Jones;[11] Möller and Lundsgaard;[12] Fishberg[13]). Fishberg, in discussing tests of renal function in hypertension, stated: "The phenolsulfonphthalein output is more frequently subnormal (than the results of concentration tests) but this is more often the result of cardiac weakness than of impairment of renal function." MacKay,[14] studying the diurnal variation in urea clearance, found it most pronounced in patients with arteriosclerotic Bright's disease. This he attributed to hypersensitivity of response of the vascular system to stimuli in this disease. Stewart and McIntosh[15] studied the renal function of 38 patients with various types of compensated cardiac lesions. The urea clearance was low in 8 of the 38 patients; the phenolsulfonphthalein output was low in only 1. Nineteen of 20 patients with arteriosclerotic or hypertensive heart disease had impaired renal function. Of 15 patients who had previously suffered from congestive heart failure, all had a normal urea clearance and phenolsulfonphthalein excretion, but only 2 were able to concentrate and dilute well. Coincident with improvement in cardiac reserve, a return of renal function toward normal was frequently observed. Brems and Nielsen[16] have noted depression of the urea and creatinine clearance well below normal in patients with mild circulatory stasis. The presence of hypertension did not appreciably influence the results.

In patients with hypertension and weakness of the left ventricle, we have been struck by the frequent occurrence of a renal symptom, nocturia. It often precedes by a short interval or accompanies the appearance of such symptoms as breathlessness on exertion, paroxysmal nocturnal dyspnea, anginoid pains and oppression and cough, in the absence of signs of peripheral or abdominal venous stasis. It frequently disappears under a regimen of rest and digitalis. This symptom

11. Hopkins, A. H., and Jones, L.: Studies in Renal Function, with Special Reference to Nonprotein Nitrogen and Sugar Concentration in the Blood, Phenolsulphonphthalein Elimination and Blood Pressure, Arch. Int. Med. **15**:964 (June) 1915.

12. Möller, E., and Lundsgaard, C.: Investigations into the Value of the Phenolsulphonphthalein Test in Renal and Circulatory Diseases, Acta med. Scandinav. **63**:242, 1926.

13. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1931, p. 543.

14. MacKay, E. M.: The Diurnal Variation of Urea Excretion in Normal Individuals and Patients with Bright's Disease, J. Clin. Investigation **6**:505 (Dec.) 1928.

15. Stewart, H. J., and McIntosh, J. F.: The Function of the Kidneys in Patients Suffering from Cardiac Disease Without Signs of Heart Failure, J. Clin. Investigation **6**:325 (Oct.) 1928.

16. Brems, A., and Nielsen, E.: Investigations on Kidney Function in Patients with Heart Ailments, Bibliot. f. læger **125**:266 (July) 1933; abstr., J. A. M. A. **101**:1280 (Oct. 14) 1933.

has received scant attention in the American literature regarding weakness of the left side of the heart, but it has been stressed on the Continent as an early and important indication of impending failure of the left ventricle (Munk, Leberman,[9] Volhard and Suter[5]). According to Volhard and Suter, it is to be distinguished from the nocturia of renal insufficiency by the fact that it is accompanied by oliguria during the day, is influenced by the fluid intake and varies with the integrity of cardiac function.

Of our series of 111 patients with hypertension, 21 presented the clinical picture of weakness of the left ventricle. The phenolsulfonphthalein excretion was not depressed in this group (it averaged 63 per cent, with 5 values below 55 per cent) as compared with an average of 61 per cent for the patients with good cardiac function. Unfortunately, only 5 determinations of urea clearance were conducted on the patients with cardiac disease. However, the urea clearance was less than 65 per cent of normal in all these patients, the highest clearance being 62 per cent and the lowest 54 per cent. Of 8 tests of creatinine excretion, 4 gave abnormally low results according to our criteria. These results apparently indicate that the phenolsulfonphthalein output is less influenced by cardiac weakness than is the outcome of other tests.

The response to the Volhard water test by patients with weakness of the left ventricle showed statistically significant deviations both from the normal value and from the response observed in patients with hypertension having a good myocardial reserve. The average volume of urine elaborated during the four hour period after the ingestion of water by the patients with cardiac weakness was 375 ± 41 cc. For the same period, normal persons excreted an average volume of 648 ± 34.6 cc., and patients with noncardiac hypertensive disease, an average volume of 525 ± 35 cc. These results are expressed as distributions in chart 1. The lag in the excretion of water by these patients was usually compensated for by an increase in the volume of urine during the afternoon period of the test, so that under these controlled conditions their total output for the twelve-hour day and night intervals often did not vary appreciably from the normal. However, this difference in the rate of formation of urine helps to explain the nocturia shown by such patients under normal conditions. The delay in the diuretic response to fluids consumed during the latter part of the day necessarily results in an increase in the amount of urine passed during the night if the fluid is not to be retained in the form of edema. We offer a hypothetic explanation for this phenomenon. Normally the venous pressure rises in response to physical activity, but the unimpaired heart muscle responds so adequately to this burden that the rise is transitory and circulatory stasis

does not occur.[17] If the myocardial reserve is reduced, the rise in venous pressure in response to exertion may be excessive and the period of recovery following activity may be prolonged, so that during the day some degree of venous stasis and a consequent tendency to the formation of edema may be present most of the time. Ingested fluids may in part escape into the tissues as occult edema and not reach the kidneys for excretion. When the patient goes to bed, the venous pressure returns to normal and remains so, and the tendency toward formation of edema is consequently dissipated. Nocturnal diuresis of retained fluids might well result.

We are at present studying the question of lag of excretion of water in patients with weakness of the left ventricle other than that associated with hypertension. In the cases so far observed, a similar

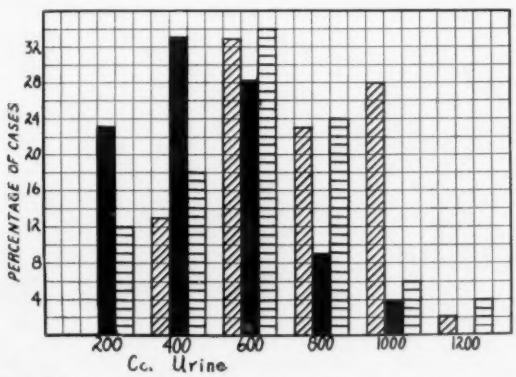

Chart 1.—Distribution of the volumes of four hour specimens of urine after the ingestion of 1,000 cc. of water. The diagonal-shaded blocks indicate the specimens from normal subjects; the solid blocks indicate those from patients who had hypertension and weakness of the left ventricle, and the horizontal-shaded blocks indicate those from patients with hypertension and a good myocardial reserve.

delay in the excretion of water is demonstrable. We believe that nocturnal polyuria, when present without obvious cause in such persons, should be regarded as of cardiac origin and that it is not without diagnostic significance.

In addition to impairment of diuretic response, it was found that in many of the hypertensive patients with left ventricular fatigue there was failure to elaborate urine of normally high specific gravity during the afternoon period of the Volhard test. In normal persons a specific

17. Eyster, J. A. E., and Meek, W. J.: Studies on Venous Pressure, Am. J. Physiol. **95**:294 (Nov.) 1930.

gravity of 1.027 ± 0.0008 was reached. Hypertensive patients with a good cardiac reserve had an average specific gravity of 1.025 ± 0.001, while in those with cardiac weakness the value was lowered to an average of 1.022 ± 0.0014. Distributions are expressed in chart 2. Analysis showed that this inability to concentrate normally was independent of the slightly increased afternoon urinary volume encountered in many of these patients. Strauss [18] called attention to this phenomenon as an indication of beginning circulatory insufficiency. We have observed that the concentrating ability, as measured by this technic, improves coincidentally with the disappearance of cardiac symptoms. In these instances it appears that we are demonstrating by this test a disturbance of the renal circulation rather than an actual decrease in the amount of functioning parenchyma.

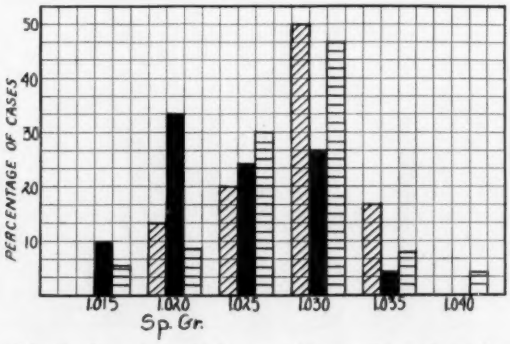

Chart 2.—Distribution of the highest specific gravities of specimens collected in the afternoon period of the Volhard test. Diagonal shading indicates the specimens from normal persons; solid shading indicates the specimens from persons with hypertension and weakness of the left ventricle, and horizontal shading indicates specimens from patients with hypertension and a good myocardial reserve.

COMMENT

We may conclude from these studies that a judgment based on the functional examinations at our command concerning the actual amount of unscarred renal parenchyma in a patient with hypertension is a difficult undertaking. We cannot separate the kidney from a constantly changing circulatory environment, on which its functional response must in great measure depend. To produce conditions under which the response to a functional burden is measured and at the same time an unchanging renal circulation obtains is too much to hope for in

18. Strauss, H.: Zur Diagnose beginnender Kreislaufinsuffizienz, Deutsche med. Wchnschr. **58**:926 (June 10) 1932.

the hypertensive patient. Such factors as changing vascular tone and decreased cardiac reserve introduce variables difficult of evaluation. The more sensitive the test of function, the more may it be influenced by these factors and, therefore, the more difficult is the interpretation in terms of renal pathology. That these tests allow one to draw conclusions regarding impairment primarily of either glomerular or tubular function in persons with hypertension, as some observers[19] have suggested, is extremely unlikely. It is, furthermore, obvious from this study that statistical conclusions regarding the incidence of faulty renal function in patients with hypertension will vary so greatly with the tests used and with the manner of their interpretation as to mean little or nothing.

As to judging the individual merits of the tests utilized in this study, we are confronted by a lack of an absolute standard for comparison of worth, and the indefinite correlation between the results of these various measurements makes the task yet more difficult. Forced to a choice, we suggest that the phenolsulfonphthalein test and the water test of Volhard are to be preferred in cases of arteriosclerotic renal disease. They are economically and easily performed. They work little hardship on the patient. The phenolsulfonphthalein excretion appears to be the function least influenced by circulatory stasis, and it correlates more closely with the urea nitrogen level of the blood than do the functions measured by the other tests. The response to the water test of Volhard, on the other hand, may be interpreted in terms both of cardiac fatigue and of impairment of renal function. With more detailed study and refinement in technic, it may be hoped that this test will throw a clearer light on the functional interrelationship of the heart and the kidneys in persons with arteriosclerotic Bright's disease.

In answer to the question suggested at the beginning of this paper —How may one predict that a patient with hypertension will or will not die of uremia?—we agree wholeheartedly with Addis,[20] who said: "The truth is that none of the accepted methods of clinical examination is able to differentiate with any certainty between the small number of patients who are going to die within a year or two of renal failure and the great majority who may live for decades and die of some intercurrent disease or from cardiac decompensation or cerebral thrombosis or hemorrhage."

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19. Ellis, L. B., and Weiss, S.: Normal Variation in Renal Function Tests with Discussion of Their Physiologic Significance, Am. J. M. Sc. **176**:233 (Aug.) 1933; Renal Function in Arterial Hypertension, J. A. M. A. **100**:875 (March 25) 1933.

20. Addis, T.: The Renal Lesion in Bright's Disease, New York, Paul B. Hoeber, Inc., 1931, p. 95.

SUMMARY

In 111 cases of arteriosclerotic Bright's disease renal function was measured by the phenolsulfonphthalein test and by the dilution and concentration test of Volhard. In addition, the urea clearance was determined in 33 patients, creatinine excretion (Major's test) in 34 and the urea nitrogen level of the blood in 67.

Standards of normal response to a slightly modified Volhard water test are given.

Impairment of diluting ability was present in one quarter of our patients with essential hypertension. The creatinine excretion was low in one third. Urea clearance, concentrating ability and phenolsulfonphthalein output were each low in one half of the patients on whom these measurements were made.

Correlation between the results of the tests was vague and little better than could be expected as a chance occurrence. In the individual instance, it was impossible in this study to predict the outcome, as regarded normality of response by our criteria, of any one test on the basis of the result given by another. A possible exception to this was that an increased amount of urea nitrogen in the blood was usually accompanied by a decreased output of phenolsulfonphthalein.

The effect of weakness of the left ventricle on the results of the tests was studied in 21 instances. The phenolsulfonphthalein output was not apparently decreased; the urea clearance was. By the Volhard technic, a lag in the excretion of water and an impairment of concentrating ability were demonstrated in these patients.

The significance of nocturia in patients with weakness of the left side of the heart, traceable to a delay in the diuretic response to fluids consumed in the latter part of the day, is discussed. A hypothetic explanation for this phenomenon is offered. When shown without obvious cause by such patients, nocturnal polyuria is primarily of cardiac origin, and its presence may be of value in the diagnosis of impending failure of the left ventricle.

It is difficult to interpret the results of tests of renal function in persons with arteriosclerotic renal disease in terms of the actual amount of healthy renal parenchyma. The value of the available tests as an aid to prognosis is disappointing.

THE DIFFERENTIAL PLATELET COUNT

ITS CLINICAL SIGNIFICANCE

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Numerous observations have been made on the total thrombocyte count in health and in disease. The differential platelet count, on the other hand, has thus far received little attention. In this investigation the behavior of the total and differential platelet counts in a number of important clinical conditions was studied and an attempt was made to analyze the results from the standpoint of their clinical significance.

Until recently the methods employed for differential platelet counting involved the use of dry stained blood films. This procedure, though simple, is inaccurate, since many of the platelets are washed off and destroyed during the process of staining, and those remaining on the glass slides or cover slips are either torn or distorted. The most accurate method for studying the morphologic characteristics of the platelets is one in which wet preparations are employed. The diluting fluid must preserve the platelets for a sufficiently long period, at least two hours, to allow an accurate total and differential count.

METHOD

The preserving fluid employed in this investigation for both total and differential platelet counting has the following composition:

	Gm. or Cc.
Sodium metaphosphate	1.0
Sodium chloride	0.5
Dextrose	0.1
Distilled water	100.0

Under optimal conditions the platelets in this solution, when observed with the oil immersion lens, appear as free-floating, isolated, clear, highly refractile bodies with numerous spinelike processes projecting from the periphery. Most of the platelets are fairly round or ovoid; irregularly shaped thrombocytes, especially elongated forms considered by Aynaud [1] to be the common physiologic type, are seen rather infrequently in these

This study was made possible by a grant from the Bingham Associates Fund.
From the Medical Clinic of the Boston Dispensary, Service of Dr. Joseph H. Pratt, and the Department of Medicine, Tufts College Medical School.

1. Aynaud, M.: La globuline des mammifères, Thèse de Paris, no. 93, 1909.

preparations. If it is desirable to stain the platelets the following solution may be used:

	Gm. or Cc.
Sodium metaphosphate	1.00
Sodium chloride	0.40
Dextrose	0.10
Sodium bicarbonate	0.10
Brilliant cresyl blue	0.15
Distilled water	100.0

The technic employed for the enumeration of the platelets is described by me in detail elsewhere.[2] It may be outlined briefly as follows:

The palmar surface of the finger-tip is punctured with an automatic lancet after thorough cleansing of the parts with soap and water and subsequent drying with alcohol and ether. The first drop or 2 of blood is discarded. A drop of the diluting fluid is then placed over the puncture wound before the blood reaches the surface of the skin, and the hand is quickly turned over so that the palmar surface is directed downward. After a sufficiently large drop of blood has escaped into the drop of diluent, the mixture is applied to the surface of a small quantity (3 or 4 drops) of diluting fluid contained in a paraffin cup. The mixture is gently stirred and then transferred by means of a paraffin-coated applicator to a glass slide; usually three preparations can be obtained, as the quantity of fluid in the cup yields 3 large drops. A cover slip is placed over each drop, and after the preparations have been allowed to stand for from ten to fifteen minutes a relative thrombocyte-erythrocyte count is made, the oil immersion lens being used. Sealing the edges of the preparations with liquid petrolatum will prevent air currents in them. An erythrocyte count is then done in the usual manner, and the absolute number of platelets per cubic millimeter is determined. With this method the average number of platelets per cubic millimeter in normal adults is about 500,000.

The size of the platelets was estimated in a manner similar to that used in the determination of the average diameter of red cells. The procedure was carried out simultaneously with the enumeration of the thrombocytes. The morphologic picture of the platelets was noted in each preparation until a total of about 200 thrombocytes had been observed. At first an ocular micrometer was employed, and after some experience had been gained in determining the diameter of the platelets their size was estimated by comparison with the average normal erythrocyte.

THE DIFFERENTIAL PLATELET COUNT IN HEALTH

The average diameter of normal platelets as reported by most investigators is approximately 2.5 microns. However, the platelets as observed in wet preparations vary considerably in size. They can generally be divided into four distinct groups: group 1, consisting of plate-

2. Olef, I.: The Enumeration of Blood Platelets, J. Lab. & Clin. Med. **20**:416 (Jan.) 1935.

lets the diameter of which is one-quarter that of a red cell, or about 1.8 microns; group 2, consisting of platelets with a diameter one-third that of a red cell, or about 2.5 microns; group 3, consisting of platelets with a diameter one-half that of a red cell or greater, or about 3.6 microns, and group 4, consisting of irregular-shaped platelets. The differential formulas for platelets of forty-five normal adults, determined by the technic just described, yielded the following averages: group 1, 18.6 per cent; group 2, 63.3 per cent; group 3, 17.4 per cent; group 4, 0.7 per cent. In 70 per cent of the counts the platelets in group 1 ranged between 10 and 30 per cent; those in group 2, between 50 and 75 per cent, and those in group 3, between 10 and 30 per cent. Approximately one fifth of all the platelets, therefore, belong to group 1, or the small variety, most of the remaining platelets having a diameter

TABLE 1.—*Differential Platelet Counts as Determined in Wet Preparations by Various Authors*

Author	Percentage Group 1	2	3	4	Preserving Fluid
Degkwitz: Folia haemat. **25**: 153, 1919-1920	....	94.4	5.6	...	Sodium metaphosphate
Nygaard: Proc. Staff Meet., Mayo Clinic **9**: 492 (Aug. 15) 1934	10.0	85.0	5.0	...	1.6% solution of sodium oxalate
Boshamer: Ztschr. f. d. ges. exper. Med. **48**: 631, 1925-1926	17.0	74.0	4.0	5.0	14% solution of magnesium sulfate
Boshamer: Ibid.	49.0	43.0	3.5	4.5	Tyrode's solution
Horwitz: Ztschr. f. d. ges. exper. Med. **57**: 280, 1927	49.6	30.0	19.7	0.7	Tyrode's solution
Horwitz: Klin. Wchnschr. **10**: 1613 (Aug. 29) 1931	70.0	30.0	....	0.5-1.0	Tyrode's solution

one-third that of a red cell or greater. I have never observed giant platelets, i. e., those the size of a red cell or larger, in normal human blood, although Stahl [3] claims to have seen them.

Table 1 represents the differential platelet counts as determined in wet preparations by various investigators.

Apparently the differential formula obtained with Tyrode's solution yields high values of small platelets, i. e., those belonging to group 1. In fact, all investigators employing this diluent gave the average diameter of normal platelets as varying from one-eighth to one-half that of a red cell. This physiologic solution introduced by Tyrode [4] in 1910 is a good artificial nourishing fluid but a poor preservative of platelets. In this solution, after a relatively short time, from twenty to thirty minutes, it may be observed that the smaller platelets increase in number

3. Stahl, R.: Ueber die Blutplättchen bei Infektions- und Blutkrankheiten, insbesondere über die unreifen pathologischen Plättchenformen (Thromboblasten), Ztschr. f. klin. Med. **96**:182, 1923.

4. Tyrode, M. V.: The Mode of Action of Some Purgative Salts, Arch. internat. de pharmacol. **20**:205, 1910.

as the larger forms diminish. Evidently the increase in the number of the smaller platelets is due to the rather rapid disintegration of the larger types. Many of these small platelets are microthromocytes 1 micron or even less in diameter. There has been considerable controversy as to the nature of these diminutive bodies.[2] From my own observations and those of many other investigators, it is highly probable that they represent either products of disintegration of platelets or other artefacts the nature of which is uncertain. The differential platelet count as obtained with this solution is therefore inaccurate. Zeller,[5] who employed Kemp and Calhoun's[6] diluting fluid, described the size of

TABLE 2.—*Comparative Differential Platelet Counts*

Percentage Groups					
1	2	3	4	Preserving Fluid	Comments
8.3	63.6	23.9	4.2	My solution	Blood from normal adult
26.4	52.0	19.0	2.6	3.6% solution of sodium citrate	
18.8	60.0	19.4	1.9	My solution	Blood from normal adult
67.2	32.8	0	0	3.6% solution of sodium citrate	
51.3	43.4	5.3	0	0.85% solution of sodium chloride	
23.4	63.5	11.2	2.0	My solution	Blood from normal adult
60.0	35.0	5.0	0	Tyrode's solution	
57.6	37.2	1.6	3.6	My solution; 408,000 platelets per cu.mm.	Amputation of foot on twentieth postoperative day (patient 46, table 10)
51.2	42.0	2.6	4.2	1.6% solution of sodium oxalate; 333,000 platelets per cu.mm.	
2.0	17.0	81.0	0	My solution; 224,000 platelets per cu.mm.	Chronic thrombocytopenic purpura (patient 29, table 7)
28.0	55.0	17.0	0	Dried blood films stained with Wright's stain; 125,000 platelets per cu.mm.	
4.5	39.1	54.3	2.1	My solution; 257,000 platelets per cu.mm.	Hemochromatosis (patient 54, table 11)
67.9	25.4	6.7	0	Dried blood films stained with Wright's stain; 340,000 platelets per cu.mm.	

the platelets as varying from the diameter of a red cell to the size of a pinpoint. I have never observed such marked morphologic variations of the platelets in normal blood.

Table 2 shows the simultaneous comparative observations on the same blood in the solution of sodium metaphosphate, Tyrode's solution, isotonic solution of sodium citrate (3.6 per cent), isotonic solution of sodium oxalate (1.6 per cent) and physiologic solution of sodium chloride (0.85 per cent). Only the results obtained with the solution of sodium oxalate compare favorably with those obtained with the solution of sodium metaphosphate, although the total platelet count with the former diluent is lower. Included in this table are also the comparative

5. Zeller, H.: Neue Methode der Bluttplättchenzählung nebst einigen Resultaten, Ztschr. f. d. ges. exper. Med. **10**:103, 1919.

6. Kemp, G. T., and Calhoun, H.: Enumeration of Blood Platelets: Their Relation and That of the Leukocytes to Blood Coagulation, Brit. M. J. **2**:1539 (Nov. 23) 1901.

observations obtained from dry stained blood films. The blood from patients 29 and 54 presented in wet preparations considerable numbers of large and giant platelets, which were markedly reduced in the dry preparations.

THE DIFFERENTIAL PLATELET COUNT IN DISEASE

Anemia.—In chronic anemia, both secondary and primary, the platelet count is usually reduced, although it may be nearly normal (patient 1, table 3). The differential formula may be either normal or abnormal. The deviation from the normal in the differential platelet count is usually due to the presence of increased numbers of small platelets, i. e., those belonging to group 1. As the total count rises the number of small platelets increases until the normal level is reached, when the differential formula also gradually reverts to normal. The total thrombocyte and differential counts, therefore, are normal if the anemia has been under adequate treatment (with iron or liver) for a sufficiently long period (patients 3, 5, 6, 8, 9, 10). Patients 1 and 2 exhibited

TABLE 3.—*Differential Platelet Count in Anemia*

Patient	Sex	Age	Platelets per Cu.mm.	Differential Platelet Formula (in Percentage)				Comment	Diagnosis
				Group 1	Group 2	Group 3	Group 4		
1	F	40	450,000	24.0	44.0	30.0	2.0	1 per cent of platelets the size of a red cell	Severe secondary anemia due to bleeding hemorrhoids
2	M	42	281,000	8.3	45.9	44.9	0.9	Numerous large platelets, many giant platelets	Primary hypochromic anemia; bleeding hemorrhoids
3	M	33	250,000	29.2	39.8	27.7	3.3	.....	Chronic bleeding peptic ulcer; red cell count, 2,290,000
			488,000	36.4	50.0	12.5	1.1	... .	1 month later, red cell count, 5,420,000
4	M	19	437,000	15.0	73.5	10.6	0.9	.. ..	Normal
			372,000	49.0	45.0	4.0	2.0	....	20 hours after removal of 500 cc. of blood for transfusion
			677,000	66.0	30.5	3.5	...	.....	5 days later
5	M	56	293,000	14.7	55.4	27.4	2.5	....	Primary hypochromic anemia
			451,000	22.7	56.4	20.0	0.9	.....	After 1 month with iron treatment
6	F	41	547,000	22.0	66.0	12.0	...	.....	Primary hypochromic anemia under iron treatment
7	F	42	382,000	8.1	63.8	22.5	5.6	... .	Primary hypochromic anemia
8	M	68	149,000	55.3	37.5	5.4	1.8	.....	Pernicious anemia, red cell count, 2,200,000
			508,000	32.2	47.1	20.7	...	....	After 9 months' treatment with liver extract, red cell count, 5,050,000
9	M	37	421,000	19.4	62.5	18.1	...	. ...	Pernicious anemia under liver treatment
10	F	40	512,000	10.0	85.0	5.0	...	.....	Pernicious anemia under liver treatment

abnormal bone marrow reactions as judged by the presence of giant platelets in the peripheral blood. Hayem [7] and Nattan-Larrier [8] also observed giant platelets in chronic anemias.

In the anemias due to acute loss of blood there is usually an increase in platelets following an initial drop. The differential formula is abnormal, owing to the presence of many small forms. This is illustrated by chart 1, for patient 4, who acted as a donor for a blood transfusion. Degkwitz,[9] however, noted giant platelets in this condition. Thrombocytosis following acute loss of blood has been observed by Mackay,[10] Richardson [11] and Clough,[12] and is, according to Hartung,[13] a factor of

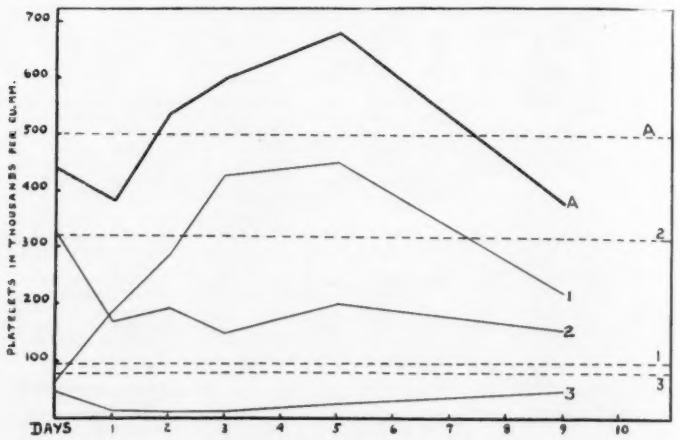

Chart 1 (patient 4).—Behavior of platelets following acute loss of blood. In all the charts the dotted line *A* represents the normal platelet level, and the dotted lines *1, 2* and *3,* the normal absolute levels of the corresponding groups. The continuous line *A* represents the behavior of the total platelet count, and the continuous lines *1, 2* and *3,* that of the absolute counts of the corresponding groups.

7. Hayem, G.: Leçons sur les maladies du sang, Paris, G. Masson, 1900.

8. Nattan-Larrier, L.: Sur quelques caractères morphologiques des hémoblastes, Compt. rend. Soc. de biol. **63**:771 (Dec. 28) 1907.

9. Degkwitz, R.: Studien über Blutplättchen, Folia haemat. **25**:153, 1919-1920.

10. Mackay, W.: The Blood Platelet: Its Clinical Significance, Quart. J. Med. **24**:285 (April) 1931.

11. Richardson, F. L.: Effect of Severe Hemorrhage on the Number of Blood Plates in Blood from the Peripheral Circulation of Rabbits, J. M. Research **8**:99, 1904-1905.

12. Clough, P. W.: Diseases of the Blood, New York, Harper & Brothers, 1929.

13. Hartung, D.: Zur Verhütung der Thrombose und Embolie, Deutsche Ztschr. f. Chir. **229**:271, 1930.

some importance in the predisposition to the development of spontaneous thrombosis as seen postoperatively and in patients with polycythaemia vera treated with phenylhydrazine and venesection or with venesection alone.

Polycythaemia Vera.—Thrombocytosis is frequently encountered in this condition (table 4); the total platelet count, however, may be normal or reduced. The abnormality in the differential formula is due either to a shift to the left, owing to the appearance of increased numbers of small platelets (patients 11, 12 and 15), or to a shift to the right, owing to the presence of large and giant platelets (patient 14). Barta [14] observed giant platelets in the dry stained blood smears obtained from patients with this condition, and Minot [15] noted megakaryocytes in these smears.

TABLE 4.—*Differential Platelet Count in Polycythaemia Vera*

Patient	Sex	Age	Platelets per Cu.Mm.	Differential Platelet Formula (in Percentage)				Comment	Treatment
				Group 1	Group 2	Group 3	Group 4		
11	F	33	637,000	48.0	45.0	7.0	...	.....	.....
12	M	37	292,000	45.0	48.0	7.0	...	.....	.....
13	F	50	581,000	25.8	41.0	33.2	...	.....	.....
14	M	60	462,000	25.0	40.0	35.0	...	Many large platelets	Phenylhydrazine
15	F	50	900,000	42.6	41.7	6.1	9.6	.....	Phenylhydrazine

The total and differential platelet counts at times assume considerable importance by affording criteria as to the type of treatment to be employed in this disease. Patients with polycythaemia vera occasionally exhibit a tendency to the development of spontaneous thrombosis, especially after treatment with phenylhydrazine and venesection. It is well known that phenylhydrazine, when administered to these patients, frequently causes an increase in the number of platelets, often to a high level. That phenylhydrazine may cause extreme thrombocytosis by irritating the giant cells of bone marrow is evident from the observations of Frey,[16] who noted that the highest number of megakaryocytes ocurred in the bone marrow of a patient with polycythaemia vera (6,457 megakaryocytes per cubic millimeter in the marrow of the femur instead of

14. Barta, I.: Beitrag zur Entstehung der Thrombose bei Polyzythämie nach Phenylhydrazinbehandlung, Deutsches Arch. f. klin. Med. **162**:185, 1928.

15. Minot, G. R.: Megakaryocytes in the Peripheral Circulation, J. Exper. Med. **36**:1 (July) 1922.

16. Frey, H. C.: Das Verhalten der Megakaryozyten im menschlichen Knochenmark und deren Beziehungen zum Gesamtorganismus, Frankfurt. Ztschr. f. Path. **36**:419, 1928.

from 200 to 250 megakaryocytes found normally). The observations of Gáspár [17] agree with those of Frey. In fact, the highest platelet count in man reported in the literature occurred in a patient with polycythemia who was treated with phenylhydrazine, in whom the count rose to 3,100,000 per cubic millimeter (Jürgens and Bach [18]). The phenylhydrazine thrombocytosis is frequently associated with the presence of numerous small platelets, which have been observed by Barta,[14] Zeller,[19] Jürgens and Naumann [20] and Jürgens [21] to agglutinate readily. These two factors, extreme thrombocytosis and increased agglutinability of the platelets, create conditions favoring the development of spontaneous thrombosis in these patients. A similar reaction is noted after venesection, as has been emphasized by Hartung.[13] Therefore, the suggestion of Falconer [22] that polycythemia be treated with phenylhydrazine and venesection may be a rather dangerous therapeutic procedure in patients whose platelet count is considerably elevated. For patients exhibiting marked thrombocytosis associated with the presence of large numbers of small platelets the safest form of treatment is roentgen irradiation.

Leukemia.—In chronic lymphatic leukemia (table 5) the total thrombocyte count is usually reduced. However, it may be normal (patient 19). Thrombopenia is the rule in the aleukemic leukoses. In chronic myelogenous leukemia the total platelet count is usually elevated, often to a moderately high level. Stahl,[3] however, observed relatively slight increases in the number of platelets in myelogenous leukemia. His results can be ascribed to the employment of Fonio's [23] inaccurate method for the enumeration of platelets.

The deviation from the normal in the differential platelet count in leukemia is usually due to the presence of many small platelets. In myelogenous leukemia, in addition, large and giant platelets are fre-

17. Gáspár, S.: Untersuchungen über Ursprung, Zahl und Form der Blutplättchen und über das Benehmen der Knochenmarksriesenzellen (Megakaryozyten) unter normalen und pathologischen Verhältnissen, Frankfurt. Ztschr. f. Path. **34**:460, 1926.

18. Jürgens, R., and Bach, K.: Thrombosebereitschaft bei Polycythaemia Vera, Deutsches Arch. f. klin. Med. **176**:726 (Aug.) 1934.

19. Zeller, H.: Die Differenzierung der Blutplättchen, Deutsche med. Wchnschr. **47**:505 (May 5) 1921.

20. Jürgens, R., and Naumann, W.: Klinische und experimentelle Untersuchungen über Funktionen der Blutplättchen, Deutsches Arch. f. klin. Med. **172**: 248 (Dec.) 1931.

21. Jürgens, R.: Beitrag zur Pathologie und Klinik der Blutungsbereitschaft, Ztschr. f. klin. Med. **123**:649, 1933.

22. Falconer, E. H.: Treatment of Polycythemia: The Reticulocyte Response to Venesection, Phenylhydrazin and Radiation, Ann. Int. Med. **7**:172 (Aug.) 1933.

23. Fonio, A.: Ueber ein neues Verfahren der Blutplättchenzählung, Deutsche Ztschr. f. Chir. **117**:176 (June) 1912.

quently found (patients 17 and 18). Abnormally large platelets in myelogenous leukemia have also been noted by Degkwitz,[9] Hayem[7] and Puchberger.[24] Minot[15] and Minot and Buckman,[25] moreover, observed various-sized megakaryocytes in dry stained blood smears obtained from patients with this condition.

Malignant Growths.—In patients with a malignant growth (table 6) the total platelet count is frequently elevated; however, it may also be normal or reduced. Marked thrombopenia, on the other hand, is rare and usually indicates invasion of bone marrow by the malignant process. The abnormality in the differential formula is due either to an increase in the number of small forms or to the presence of large and giant platelets.

TABLE 5.—*Differential Platelet Count in Leukemia*

Patient	Sex	Age	Platelets per Cu.Mm.	Differential Platelet Formula (in Percentage)				Comment	Diagnosis
				Group 1	Group 2	Group 3	Group 4		
16	M	46	736,000	37.8	45.4	5.9	10.9	.....	Chronic myelogenous leukemia
			548,000	45.8	46.4	7.8	...	.....	After roentgen treatment
17	F	56	1,319,000	40.0	40.0	18.0	2.0	Many large platelets	Chronic myelogenous leukemia
18	F	42	252,000	32.8	50.4	16.8	...	Occasional giant platelets	Aleukemic myelogenous leukemia
19	M	38	465,000	9.0	64.5	24.0	2.5	.....	Chronic lymphatic leukemia
20	F	60	179,000	63.0	34.0	3.0	...	.....	Aleukemic lymphatic leukemia

In a patient with Hodgkin's disease (patient 28) the thrombocytosis present was associated with a fairly normal differential formula. Following treatment with roentgen irradiation there was a drop in the total count, and then a rise above the initial level, with the simultaneous appearance of large numbers of small platelets. Thrombocytosis in Hodgkin's disease has been noted also by Minot,[15] Bunting[26] and Crawford;[27] the former two investigators, in addition, have observed many giant platelets and megakaryocytes in dry stained blood films.

24. Puchberger, G.: Bemerkungen zur vitalen Färbung der Blutplättchen des Menschen mit Brilliantkresylblau, Virchows Arch. f. path. Anat. **171**:181, 1903.

25. Minot, G. R., and Buckman, T. E.: The Blood Platelets in the Leukemias, Am. J. M. Sc. **169**:477 (April) 1925.

26. Bunting, C. H.: Blood Platelets and Megalokaryocytes in Hodgkin's Disease, Bull. Johns Hopkins Hosp. **22**:114 (April) 1911.

27. Crawford, G. J.: Blood Platelets in Anemias and Acute Infections: Their Number and Morphology, Lancet **2**:595 (Sept. 20) 1924.

The occurrence of thrombocytosis in patients with a malignant growth was first noted by Hayem [7] and is in accord with the observations of Frey [16] and Gáspár,[17] who found increased numbers of megakaryocytes in the bone marrow of these patients. The original observations of Hayem have been amply confirmed by many subsequent investigators. According to Morrison,[28] thrombocytosis is by far the most outstanding hematologic finding in cases of a malignant growth. The tendency to nonmalignant thrombosis in these cases was ascribed by Naegeli [29] to this factor. Noeff [30] expressed the opinion that thrombocytosis is found only in patients with bleeding neoplasms. Perl,[31] on the other hand, employing Fonio's method for the enumeration of platelets, found normal platelet counts in twenty-seven of thirty-three patients with a malignant growth, the remaining six exhibiting definite thrombopenia; thrombocytosis was not observed in a single instance. Marked thrombopenia is rare. Cohen [32] in 1929 reported a case and cited eight others

TABLE 6.—*Differential Platelet Count in Cases of a Malignant Growth*

Patient	Sex	Age	Platelets per Cu.Mm.	Differential Platelet Formula (in Percentage)				Comment	Diagnosis
				Group 1	Group 2	Group 3	Group 4		
21	M	60	391,000	10.0	35.0	55.0	...	Many large and giant platelets	Cancer of colon
22	M	60	375,000	27.0	64.5	8.5	...	.....	Cancer of stomach
23	M	57	721,000	16.0	49.0	35.0	...	.....	Cancer of stomach
24	F	52	1,023,000	68.7	26.5	3.1	1.7	.....	Cancer of stomach
25	F	50	385,000	12.0	40.0	48.0	...	Many large platelets, occasional giant platelets	Cancer of neck
26	F	59	601,000	56.0	36.8	5.6	1.6	.....	Cancer of breast
27	M	60	607,000	12.4	61.4	24.8	1.4	Occasional giant platelets	Cancer of lung
			469,000	45.1	45.9	9.0	...	.....	After roentgen treatment
28	M	38	677,000	23.6	54.8	21.6	...	.....	Hodgkin's disease
			627,000	35.5	47.8	16.7	...	.....	After roentgen treatment
			702,000	62.1	29.3	2.3	6.3	.....	2 months later

28. Morrison, M.: An Analysis of the Blood Picture in One Hundred Cases of Malignancy, J. Lab. & Clin. Med. **17**:1071 (Aug.) 1932.

29. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 5, Berlin, Julius Springer, 1931.

30. Noeff, K.: Neueres über die Methodik der Thrombozytenzählung und ihre praktische Verwendung insbesondere bei der Diagnose des Karzinoms, Wien. klin. Wchnschr. **48**:235 (Feb. 22) 1935.

31. Perl, C.: Die Thrombocyten beim Carcinom, Ztschr. f. klin. Med. **122**:253, 1932.

32. Cohen, J.: Het bloedbeeld bij metastatisch beenmergcarcinoom, Nederl. tijdschr. v. geneesk. **73**:5485 (Nov. 23) 1929.

from the literature. Similar cases have been reported by Rawitsch and Warschawskaja [33] and Beiglböck.[34] In fact, Beiglböck stated that in elderly patients unexplained purpura associated with thrombopenia may be the first sign of an occult cancer with metastases to bone marrow.

Abnormalities in the differential formula associated with the presence of large and giant platelets have been observed also by Rosenbaum [35] and Pelczar and Koloszynski.[36] The former investigator, moreover, expressed the opinion that the appearance of abnormally large platelets is even more characteristic than the thrombocytosis, the presence of these macrothrombocytes often being of diagnostic significance in cases in which a malignant growth is suspected.

Essential Thrombocytopenic Purpura.—The blood platelet has been described as the "guide in the labyrinth of purpuric diseases." Ever since Brohm's [37] discovery of the reduction in the number of platelets in chronic thrombocytopenic purpura, thrombopenia has been regarded as one of the most characteristic features of this disease. Normal or only slightly reduced platelet counts in cases of purpura haemorrhagica have been reported by Jones and Tocantins.[38] These cases, however, were probably instances of fibrinopenia of Rabe and Salomon,[39] of "purpura dysovarica" of Nagy [40] or of hereditary hemorrhagic thrombasthenia, which was described first by Glanzmann [41] and more recently by Jürgens.[42]

Frequently the platelets observed are too few in number for accurate differentiation. In general, however, the abnormality in the differential

33. Rawitsch, M. S., and Warschawskaja, B. B.: Zum hämatologischen Bilde der metastatischen Geschwülste, Folia haemat. **44**:150, 1931.

34. Beiglböck, W.: Ueber die Bedeutung hämorrhagischer Diathesen bei occulten Carcinomen, Ztschr. f. klin. Med. **124**:411, 1933.

35. Rosenbaum, B. N.: Zur Frage der Blutplättchen bei malignen Tumoren. Zentralbl. f. Chir. **51**:305 (Feb. 23) 1924.

36. Pelczar, K., and Koloszynski, E.: Les thrombocytes dans le cancer expérimental, Verhandl. internat. Kong. vergl. Path. **2**:514, 1931; abstr., Kongresszentralbl. f. d. ges. inn. Med. **68**:817, 1933.

37. Brohm, cited by Pratt, J. H.: Purpura and Hemophilia, in Osler, W., and McCrae, R.: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1927.

38. Jones, H. W., and Tocantins, L. M.: A Discussion of the Classification and Etiology of Purpura Hemorrhagica, M. Clin. North America **16**:181, 1932; The Treatment of Purpura Hemorrhagica, J. A. M. A. **100**:83 (Jan. 14) 1933.

39. Rabe, F., and Salomon, E.: Ueber Faserstoffmangel im Blute bei einem Falle von Hämophilie, Deutsches Arch. f. klin. Med. **132**:240 (May) 1920.

40. Nagy, G.: Ist es berechtigt, im Rahmen der hämorrhagischen Diathesen eine "Purpura Dysovarica" als selbständiges Krankheitsbild anzunehmen? Ztschr. f. klin. Med. **102**:284, 1925.

41. Glanzmann, E.: Hereditäre hämorrhagische Thromboasthenie: Ein Beitrag zur Pathologie der Blutplättchen, Jahrb. f. Kinderh. **88**:1 and 113, 1918.

42. Jürgens, R.: Ueber erbliche Thrombopathien, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **46**:104, 1934.

count is due either to the presence of many large and giant platelets or to a relative increase in the smaller forms (table 7). Hess [43] likewise stated that in purpura the morphologic picture of the platelets is abnormal, owing to the presence of macrothrombocytes and microthrombocytes. This is at variance with the observations of Nygaard [44] that in purpura from 40 to 90 per cent of the platelets belong to his group 1, or the small variety (about 1.5 microns in diameter). There was usually a tendency for the differential formula to remain abnormal in one direction, either by a shift to the right toward the larger forms or by a shift to the left toward the smaller types, even after the total platelet count had risen to a considerably high level. Thus, in patient 29, 1.5 per cent of all the platelets were in group 1 when the count was 127,000 per

TABLE 7.—*Differential Platelet Count in Chronic Thrombocytopenic Purpura*

Patient	Sex	Age	Platelets per Cu.Mm.	Differential Platelet Formula (in Percentage)				Comment	Treatment
				Group 1	Group 2	Group 3	Group 4		
29	M	25	127,000	1.0	15.0	84.0	...	Numerous giant platelets	.....
			424,000	5.0	20.0	75.0	...	Numerous giant platelets	2 months later, after having received 3 blood transfusions
30	F	27	70,000	33.3	61.3	5.4	...	Occasional giant platelets	.....
			314,000	40.0	46.0	6.0	8.0	... .	After 2 months' treatment with a high protein and high fat diet
			370,000	33.0	36.0	28.0	3.0	.....	4 months later
31	F	31	62,000	20.0	50.0	30.0	...	.....	.....

cubic millimeter, and 5 per cent of the platelets were in the same group after the count had increased to 424,000. Likewise, in patient 30 there was a considerable proportion of small thrombocytes (33 per cent) when the total count was 70,000 per cubic millimeter and a similar proportion of platelets in the same group after the count had risen to 370,000.

There seems to be a relation between the morphologic picture of the platelets and the function that they exhibit. Platelets of normal morphologic characteristics may or may not possess abnormal function; platelets of abnormal morphologic characteristics, however, always pos-

43. Hess, A. F.: The Blood and Blood Vessels in Hemophilia and Other Hemorrhagic Diseases, Arch. Int. Med. **17**:203 (Feb.) 1916.

44. Nygaard, K. K.: A Direct Method of Counting Platelets in Oxalated Plasma, Proc. Staff Meet., Mayo Clin. **8**:365 (June 14) 1933; Coagulability of the Blood Plasma and Changes in the Number of Platelets in Thrombocytopenic Purpura, ibid. **9**:492 (Aug. 15) 1934.

sess abnormal function. The large types of platelets are giants morphologically and dwarfs functionally. Thus, Jürgens and Naumann [20] noted in a case of essential thrombopenia many giant platelets which agglutinated poorly until after splenectomy, when many small platelets appeared, with the simultaneous shortening of the agglutination time. In patient 29 bleeding from the gastro-intestinal tract occurred whenever the platelet count dropped to 200,000 per cubic millimeter; the differential formula presented numerous large and giant, apparently poorly functioning platelets. Duke's [45] critical thrombocyte levels for hemorrhagic tendencies and Opitz and Schober's [46] critical platelet levels for clot retraction lose their relative significance when considered from this aspect, since they fail to correlate the quantitative aspects and the functional properties of the platelets.

Jaundice.—In patients with jaundice (table 8) the total platelet count is frequently reduced. The differential formula is abnormal,

TABLE 8.—*Differential Platelet Count in Jaundice*

Patient	Sex	Age	Platelets per Cu.Mm.	Differential Platelet Formula (in Percentage) Group 1	Group 2	Group 3	Group 4	Diagnosis
32	F	35	255,000	36.6	35.8	24.4	3.2	Catarrhal jaundice
			437,000	12.7	68.6	18.7	...	2 months later, patient well
33	M	30	306,000	37.0	54.0	8.0	1.0	Catarrhal jaundice
			485,000	24.0	60.0	16.0	...	1 month later, patient well
34	M	31	402,000	61.8	35.2	3.0	...	Catarrhal jaundice
35	M	23	406,000	31.0	41.0	28.0	...	Chronic hemolytic jaundice
36	F	28	265,000	34.3	50.0	13.7	...	Jaundice due to arsphenamine hepatitis
37	F	74	487,000	59.5	34.9	5.6	...	Obstructive jaundice

owing to the presence of increased numbers of small platelets. Decrease in the number of thrombocytes in jaundice has been observed also by Horwitz,[47] Blum [48] and Storz and Schlungbaum.[49] Jones and Minot,[50] however, noted in dry stained blood films from jaundiced patients that the number of platelets was normal up to the time that improvement

45. Duke, W. W.: The Behavior of the Blood Platelets in Toxemias and Hemorrhagic Diseases: A Preliminary Report, Bull. Johns Hopkins Hosp. **23**: 144 (May) 1912.

46. Opitz, H., and Schober, W.: Klinische und experimentelle Studien über die Bedeutung der Blutplättchen für die Retraktilität des Blutkuchens, Jahrb. f. Kinderh. **103**:189, 1923.

47. Horwitz, S.: Die klinische Bedeutung der Blutplättchenzählmethode nach Hofmann-Flössner, Ztschr. f. d. ges. exper. Med. **57**:380, 1927.

48. Blum, M. K.: Ueber Blutkörpercheneinschlüsse bei Ikterus gravis, Med. Klin. **20**:1577 (Nov. 9) 1924.

49. Storz, H., and Schlungbaum, H.: Ein klinischer Beitrag zur Pathologie der Blutgerinnung, Klin. Wchnschr. **12**:184 (Feb. 4) 1933.

50. Jones, C. M., and Minot, G. R.: Infectious (Catarrhal) Jaundice: An Attempt to Establish a Clinical Entity, Boston M. & S. J. **189**:531 (Oct. 18) 1923.

began, when an increase occurred, with the simultaneous appearance of many small and large platelets.

Several theories have been advanced to explain the susceptibility of jaundiced patients to bleeding, such as fibrinopenia (Whipple and Hurwitz [51]), a low serum calcium content (Buchbinder and Kern [52]), a decrease in the amount of diffusible calcium (Emerson [53]) and the accumulation in the blood of excessive amounts of cysteine and related forms of mercaptan (Carr and Foote [54]). The platelets, however, are intimately related to the coagulation of the blood and the syneresis of blood clots. It is probable that the deviation from the normal in their number and morphologic picture constitutes another contributory factor in the pathogenesis of the tendencies to bleeding exhibited by these patients.

Infection.—During acute infectious diseases the platelets behave in a characteristic manner, as illustrated in the case of patient 38 (table 9

TABLE 9.—*Differential Platelet Count in Infection*

Patient	Sex	Age	Platelets per Cu.Mm.	Differential Platelet Formula (in Percentage)				Diagnosis
				Group 1	Group 2	Group 3	Group 4	
38	M	46	320,000	10.0	60.7	29.3	...	Acute stage of lobar pneumonia
			1,344,000	52.5	37.9	5.1	4.5	Two days after crisis
39	M	15	790,000	48.5	42.7	6.2	2.6	Patient convalescing from lobar pneumonia
40	M	55	611,000	62.5	31.0	1.9	4.6	Bronchiectasis (low grade sepsis)
41	F	30	586,000	17.2	61.4	21.4	...	Pulmonary tuberculosis (slightly active)
42	F	40	658,000	57.8	37.1	3.1	3.1	Pulmonary tuberculosis (moderately active)
43	M	21	204,000	50.0	40.0	6.0	4.0	Subacute bacterial endocarditis

and chart 2). In the acute stage of the illness there is thrombopenia, followed during convalescence by thrombocytosis, which may be considerable. The differential formula is characterized by a shift to the left, owing to the appearance of numerous small platelets. I have not observed giant platelets in infectious diseases, although Degkwitz [9] and Minot [15] claim to have seen them in dry stained blood smears.

In chronic infections the total thrombocyte count may be elevated or reduced. The differential formula is abnormal, owing to the presence

51. Whipple, G. H., and Hurwitz, S. H.: Fibrinogen of the Blood as Influenced by the Liver Necrosis of Chloroform Poisoning, J. Exper. Med. **13**:136 (Jan.) 1911.

52. Buchbinder, W. C., and Kern, R.: Blood Calcium, Deficiency in Experimental Obstructive Jaundice, Am. J. Physiol. **80**:273 (May) 1927.

53. Emerson, W. C.: The Distribution of Calcium of Jaundiced and Acholic Dogs, J. Lab. & Clin. Med. **14**:122 (Nov.) 1928.

54. Carr, J. L., and Foote, F. S.: Progressive Obstructive Jaundice: Changes in Certain Elements of the Blood and Their Relation to Coagulation, Arch. Surg. **29**:277 (Aug.) 1934.

of increased numbers of small platelets. Tuberculosis presents a notable exception, for in this disease the platelets are nearly always increased in number. More significant than the thrombocytosis, however, is the differential platelet count, which in active cases exhibits a shift to the left. The thrombocytosis in tuberculosis has been observed by many early investigators, Halla,[55] Afanassiew[56] and van Emden[57] among

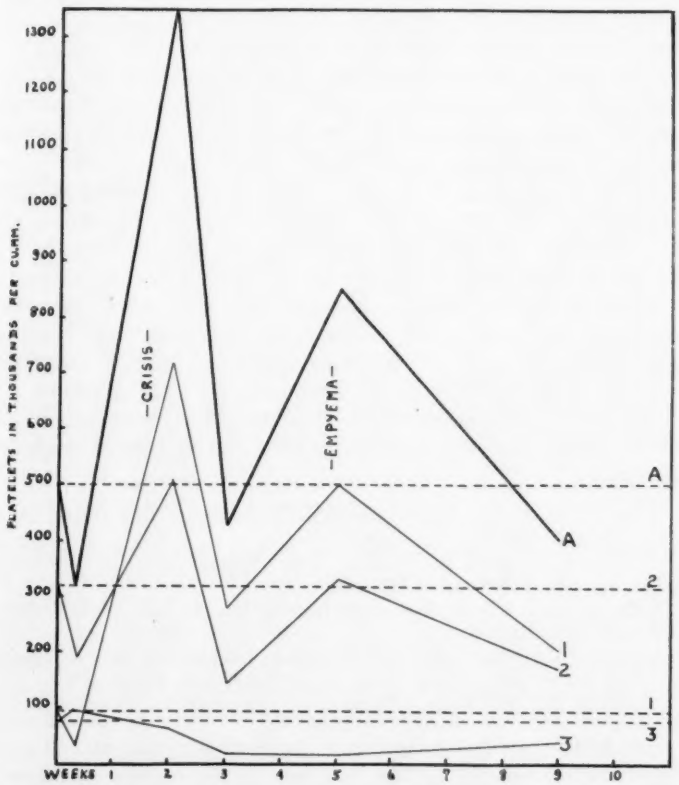

Chart 2 (patient 38).—Behavior of platelets during the course of lobar pneumonia complicated by empyema.

55. Halla, A.: Ueber den Haemoglobingehalt des Blutes und die quantitativen Verhältnisse der roten und weissen Blutkörperchen bei akuten fieberhaften Krankheiten, Ztschr. f. Heilk. **4**:331, 1883.

56. Afanassiew, M.: Ueber den dritten Formbestandtheil des Blutes im normalen und pathologischen Zustände und über die Beziehung desselben zur Regeneration des Blutes, Deutsches Arch. f. klin. Med. **35**:217 (Aug.) 1884.

57. van Emden, J. E. G.: Klinische Untersuchungen über die Blutplättchen, Fortschr. d. Med. **16**:241, 1898.

others. Bannerman,[58] Brock and Rake[59] and Brock[60] stated that the thrombocytosis is associated with activity of the tuberculous lesion and that a return to normal figures indicates a subsidence of the activity of the process; in other words, an inverse relationship appears to exist between thrombocytosis and the subject's resistance to the disease.

Hayem[61] and his pupil Reyne were first to observe the decrease in the number of platelets (*crise hématoblastique*) at the onset of acute infections. According to Hatzky,[62] this initial thrombopenia may be sufficiently severe that hemorrhagic manifestations may appear. In rheumatic fever high values for platelets have been noted at the onset (Mackay,[10] Naegeli[29] and Doenecke[63]). The platelets behave similarly in the exanthems (Glanzmann[41]). There is thrombocytosis during the incubation period of acute infectious diseases in children (Beck[64]).

The thrombopenia at the onset of acute infections is attributed to the clumping of the platelets with the micro-organisms introduced into the circulation. This phenomenon was first described by Levaditi[65] in 1901 and was interpreted by Delrez and Govaerts[66] and by Govaerts[67] as indicating that the platelets, like the leukocytes, attach themselves to foreign bodies such as bacteria, causing their destruction and removal from the circulation; if the organism introduced into the circulation is of such virulence that no agglutination with the platelets occurs, septicemia follows. The phenomenon of agglutination, therefore, is evidence of the rôle that the platelets play in aiding the body in combating infection.

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58. Bannerman, R. G.: Blood-Plate Counts in Pulmonary Tuberculosis, Lancet **2**:593 (Sept. 20) 1924.

59. Brock, R. C., and Rake, G. W.: Some Observations on Blood-Platelets, Guy's Hosp. Rep. **9**:451 (Oct.) 1929.

60. Brock, R. C.: Observations on the Platelet Count in Tuberculosis, Tubercle **15**:241 (March) 1934.

61. Hayem, G.: Recherches sur l'évolution des hématies dans le sang de l'homme et des vertébrés, Arch. de physiol. norm. et path. **5**:692, 1878.

62. Hatzky, K.: Zur Frage der akuten Thrombopenien, Folia haemat. **47**:375, 1932.

63. Doenecke, F.: Ueber die Veränderungen der Blutplättchenzahlen bei akuter diffuser Glomerulonephritis und ihre Bedeutung für die Pathogenese, Ztschr. f. klin. Med. **121**:121, 1932.

64. Beck, D.: Ueber das Verhalten der Blutplättchen bei Infektionen, Monatschr. f. Kinderh. **29**:673, 1925.

65. Levaditi, C.: Sur l'état de la cytase dans le plasma des animaux normaux, Ann. Inst. Pasteur **15**:894 (Dec.) 1901.

66. Delrez, L., and Govaerts, P.: L'intervention des globulines dans l'élimination des microbes injectés dans la circulation, Compt. rend. Soc. de biol. **81**:53 (Jan. 26) 1918.

67. Govaerts, P.: Le rôle des plaquettes sanguines dans l'immunité naturelle, Compt. rend. Soc. de biol. **82**:927 (May 31) 1919; Effets de l'injection des plaquettes lavées sur l'élimination des microbes circulant dans le sang, ibid. **85**:745 (Oct. 8) 1921.

The thrombocytosis in infectious diseases associated with the presence of numerous small, easily agglutinating platelets constitutes a significant factor in the causation of spontaneous thrombosis and embolism at times observed in these conditions.

Postoperative Thrombocytosis.—Following surgical operations the platelet count manifests a definite behavior, illustrated in the case of patient 44 (table 10 and chart 3). There is usually a decrease in the total count during the first twenty-four hours postoperatively. After this point the platelets increase in number, reaching the maximum level toward the end of the second week, and then gradually returning to normal. The entire cycle occupies about three weeks. The differential platelet formula is abnormal throughout, owing to the presence of increased numbers of small forms. This deviation from the normal in

TABLE 10.—*Postoperative Differential Platelet Count*

Patient	Sex	Age	Platelets per Cu.Mm.	Differential Platelet Formula (in Percentage)				Diagnosis
				Group 1	Group 2	Group 3	Group 4	
44	F	41	342,000	43.0	51.0	6.0	...	24 hours after cholecystectomy
			879,000	59.2	39.1	1.9	...	Sixteenth postoperative day
45	F	20	367,000	62.5	35.2	2.3	...	24 hours after thyroidectomy
			725,000	60.0	33.0	7.0	...	Tenth postoperative day
46	F	45	480,000	22.0	70.0	8.0	...	Amputation of foot; preoperative count
			901,000	69.2	22.8	6.0	2.0	Thirteenth postoperative day

the morphologic picture of the platelets persists until the total count has returned to normal, which is usually until the end of the third week postoperatively.

The postoperative behavior of the total platelet count was first described in detail by Hueck [68] and has subsequently been confirmed by other investigators. Galloway [69] noted a similar behavior of the platelets following fractures of the long bones, and Dawbarn, Earlam and Evans [70] observed a corresponding swing of the platelets following

68. Hueck, H.: Ueber Untersuchungen der Eiweisskörper des Blutes, sowie Blutplättchenzählungen, besonders nach Operationen, Deutsche med. Wchnschr. **51**:1869 (Nov. 6) 1925; Blutplättchen-Untersuchungen bei chirurgischen Erkrankungen, Deutsche Ztschr. f. Chir. **192**:322, 1925; Blutplättchenveränderungen nach Operationen, München. med. Wchnschr. **73**:173 (Jan. 22) 1926.

69. Galloway, J. F.: The Blood-Platelets After Fracture, Lancet **1**:1082 (May 16) 1931.

70. Dawbarn, R. Y.; Earlam, F., and Evans, W. H.: The Relation of the Blood Platelets to Thrombosis After Operation and Parturition, J. Path. & Bact. **31**:833 (Oct.) 1928.

parturition. On the other hand, Rosenbaum,[71] employing Fonio's method for counting platelets, failed to observe postoperative thrombocytosis following operations on women for various types of goiter; in fact, there was frequently a considerable drop in the platelet count, persisting until the succeeding menstrual period, which was at times unusually severe. This, however, is at variance with my observations on a patient with thyrotoxicosis (patient 45) who after thyroidectomy exhibited definite thrombocytosis, reaching a maximum level on the tenth postoperative day.

The postoperative deviation from the normal in the total and differential platelet counts creates a condition favoring the development of

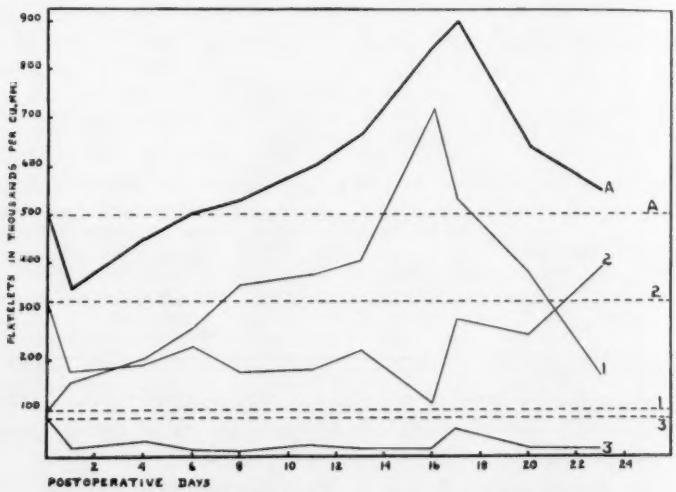

Chart 3 (patient 44).—Behavior of platelets postoperatively (following cholecystectomy).

spontaneous thrombosis and embolism. There is considerable evidence indicating that the presence of an increased platelet count is frequently associated with an increased tendency to the development of spontaneous venous thrombosis, or thrombophilia. Rosenthal,[72] for instance, observed

71. Rosenbaum, B. N.: Ueber das Verhalten der Blutplättchen bei Struma in der Vor- und Nachoperationsperiode, mit besonderer Berücksichtigung derselben zur Menstruationszeit, Zentralbl. f. Chir. **51**:2580 (Nov. 22) 1924.

72. Rosenthal, N.: Clinical and Hematologic Studies on Banti's Disease: I. The Blood Platelet Factor with Reference to Splenectomy, J. A. M. A. **84**:1887 (June 20) 1925.

certain types of splenic anemia in which the thrombocytosis following splenectomy was nearly always associated with widespread thrombosis, often ending fatally. Brock and Rake [59] noted that in certain cases of active pulmonary tuberculosis the rise in the platelet count may be associated with spontaneous venous thrombosis. The tendency to nonmalignant thrombosis in patients with cancer was ascribed by Naegeli [29] to the frequently associated thrombocytosis. Spontaneous thrombosis in patients with polycythaemia vera, especially in those under phenylhydrazine therapy, was attributed by Jürgens and Bach [18] to the associated elevation in the platelet count. Jagić and Klima [73] noted spontaneous venous thrombosis associated with the thrombocytosis following severe acute hemorrhage. Postinfectious spontaneous venous thrombosis is usually associated with the thrombocytosis observed during convalescence. Postoperatively, the clinically observed thrombosis usually occurs at the height of the rise in the number of platelets, i. e., toward the end of the second week. An important feature of the postoperative thrombocytosis is the presence of numerous small platelets which agglutinate readily. The agglutinability of the platelets, which is dependent on the magnitude of their negative electrical charge (Starlinger and Sametnik [74]), is still further increased by a number of postoperative changes in the blood plasma, such as an increase in fibrinogen and globulin (Löhr [75]) and an increase in glycolysis and in the hydrogen ion concentation of the blood (Jürgens [21] and Stuber and Lang [76]). These factors bring about a lowering of the electrostatic charge of the platelets, thereby decreasing their reciprocal electrostatic repulsion and favoring their agglutination. The thrombocytosis and the associated morphologic changes in the platelets, therefore, constitute important postoperative changes in the blood and are significant factors in the pathogenesis of postoperative thrombosis and embolism.

Miscellaneous Diseases.—Essentially normal total and differential platelet counts were observed in a patient with anaphylactoid purpura and in one with hemophilia. In chronic nephritis the total count is reduced; the differential formula is at times abnormal, owing to the

73. Jagić, N., and Klima, R.: Klinik und Therapie der Blutkrankheiten, ed. 2, Berlin, Urban & Schwarzenberg, 1934.

74. Starlinger, W., and Sametnik, S.: Ueber die Entstehungsbedingungen der Thrombose, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **39**:152, 1927.

75. Löhr, W.: Ueber Allgemeinreaktionen des Körpers bei der Wundheilung nichtinfizierter Wunden und unkomplizierter Frakturen, Deutsche Ztschr. f. Chir. **183**:1, 1923.

76. Stuber, B., and Lang, K.: Zur Pathogenese und Therapie der Thrombose, Klin. Wchnschr. **9**:1113 (June 14) 1930.

presence of increased numbers of small platelets. Doenecke [77] also found reduced numbers of platelets in chronic nephritis. In a patient with hemochromatosis the thrombopenia was associated with an extremely abnormal differential formula due to the presence of numerous large and giant platelets. Biopsy on bone marrow, performed by Dr. William Dameshek, revealed hypoplasia of the megakaryocytes. An essentially normal total platelet count was found in a patient with scurvy who had been under treatment for a short time; the abnormal differential formula due to the presence of many small platelets was suggestive of a recent preexisting thrombopenia.

TABLE 11.—*Differential Platelet Count in Miscellaneous Diseases*

Patient	Sex	Age	Platelets per Cu.Mm.	Differential Platelet Formula (in Percentage)				Comment	Diagnosis
				Group 1	Group 2	Group 3	Group 4		
47	F	32	471,000	15.3	70.3	13.7	0.7	.....	Purpura rheumatica
48	M	70	355,000	9.3	42.6	47.4	0.7	.....	Senile purpura
49	M	13	541,000	18.8	60.0	19.4	1.9	.....	Hemophilia
50	M	46	211,000	16.0	46.0	28.0	...	.....	Malignant nephrosclerosis
51	F	30	300,000	24.0	47.0	27.0	2.0	.....	Malignant nephrosclerosis
52	F	51	224,000	56.0	40.0	1.0	3.0	....	Chronic glomerulo-nephritis
53	M	15	295,000	26.6	61.1	11.2	1.2	.....	Celiac disease
54	M	59	257,000	4.5	39.1	54.3	2.1	Many large and giant platelets	Hemochromatosis
55	F	50	423,000	70.9	25.2	3.9	...	.....	Scurvy (partly treated)

THE AGE OF PLATELETS

Because of the short life cycle of the platelets (several days, according to Duke [78]), it has been rather difficult to establish satisfactory criteria for their maturity or immaturity. Basophilia of the cytoplasm of the platelets is said to indicate immaturity (Mackay [10] and Pappenheim [79]). Studies of the tinctorial features of the platelets, however, have yielded rather confusing results. The morphologic characteristics of the platelets, on the other hand, do offer some definite criteria as to their age. Degkwitz [9] noted that many large and giant platelets appeared

77. Doenecke, F.: Ueber das Verhalten der Blutplättchen bei echter Urämie, Zentralbl. f. inn. Med. **53**:580 (April 30) 1932.

78. Duke, W. W.: Causes of Variation in the Platelet Count: Experimental Results Showing the Effect of Diphtheria Toxin, Benzol and Tuberculin on the Platelet Count in Rabbits, Arch. Int. Med. **11**:100 (Jan.) 1913.

79. Pappenheim, A.: Morphologische Hämotologie, Leipzig, Werner Klinkhardt, 1919.

during the regenerative phases in conditions such as infections and loss of blood and during ultraviolet irradiation with a quartz mercury vapor lamp. Doenceke,[63] Stahl [80] and Horwitz [81] maintained that the larger platelets are immature forms. There is considerable evidence, however, that the smaller types, those belonging to group 1, are the juvenile platelets. From the observations presened in tables 3 to 11 it is apparent that during the regenerative phase the form exhibiting the greatest relative and absolute increase is usually the small platelet. Boshamer [82] and Firket [83] concluded from their experiments of injecting saponin into animals that the small platelets are the young forms. A similar opinion was expressed by Jürgens and Naumann,[20] Flössner,[84] Preiss [85] and Lampert.[86] Further support for this view is offered by the morphologic changes of the platelets following the injection of epinephrine hydrochloride. Epinephrine causes a mobilization of the formed blood elements in the peripheral circulation by bringing about a redistribution of the blood contained in the inactive blood depots of which the spleen represents a reservoir of the first order (Dameshek [87] and Rein [88]). That the spleen is a reservoir of platelets as well as of red cells has been shown by Bedson and Johnston [89] and Binet and Kaplan.[90] After the injection of epinephrine hydrochloride the volume of the spleen may become smaller by 12 per cent (Paffenholz and Schürmeyer [91]), and

80. Stahl, R.: Ueber die Notwendigkeit prinzipieller Berücksichtigung der Blutplättchen bei klinischen Blutuntersuchungen, München. med. Wchnschr. **68**: 667 (June 3) 1921.

81. Horwitz, S.: Zur Frage der physiologischen Thrombocytenzahl, Klin. Wchnschr. **12**:705 (May 6) 1933. Footnote 47.

82. Boshamer, K.: Ueber Zählung, Resistenz und Neubildung von Blutplättchen, Ztschr. f. d. ges. exper. Med. **48**:631, 1925-1926.

83. Firket, J.: Recherches sur la régéneration des plaquettes, Compt. rend. Soc. de biol. **87**:84 (May 27) 1922.

84. Flössner, O.: Beobachtungen und Zählung von Blutplättchen, Ztschr. f. Biol. **77**:113, 1922.

85. Preiss, W.: Ueber die physiologische Zahl und Morphologie der Blutplättchen, Ztschr. f. d. ges. exper. Med. **84**:810, 1932.

86. Lampert, H.: Die physikalische Seite des Blutgerinnungsproblems und ihre praktische Bedeutung, Leipzig, Georg Thieme, 1931.

87. Dameshek, W.: Physiology of the Spleen, in Piersol, G. M.: Cyclopedia of Medicine, Philadelphia, F. A. Davis Company, 1934.

88. Rein, H.: Die Blutreservoire des Menschen, Klin. Wchnschr. **12**:1 (Jan. 7) 1933.

89. Bedson, S. P., and Johnston, M. E.: Further Observations on Platelet Genesis, J. Path. & Bact. **28**:101, 1925.

90. Binet, L., and Kaplan, M.: Mobilisation des plaquettes par l'adrénaline: Plaquettose par splénocontraction adrénalique, Compt. rend. Soc. de biol. **97**:1659 (Dec. 17) 1927.

91. Paffenholz, W., and Schürmeyer, A.: Änderungen der Milz- und Lebergrösse im Röntgenbild unter verschiedenen Kreislaufbedingungen, Klin. Wchnschr. **10**:2076 (Nov. 7) 1931.

under unusual circumstances, as in the presence of splenomegaly, that organ may lose one third of its original volume (Levy [92]).

Table 12 shows the changes in the total and differential platelet counts following the subcutaneous injection of 1 cc. of epinephrine hydrochloride. It is apparent from this table that a characteristic feature of thrombocytosis due to epinephrine is the appearance of increased numbers of large platelets. These additional thrombocytes come from inactive blood reservoirs, where normally hematopoiesis does not occur. They must consequently represent platelets that have remained inactive in the blood depots, where many of them matured, and that were forced into the general circulation after the injection of epinephrine hydrochloride; they are, therefore, older or senile forms. This is in agreement with the observations of Lampson,[93] who noted that in polycythemia due to epinephrine the red cells show none of the usual reactions of

TABLE 12.—*Behavior of Platelets Before and After Injection of Epinephrine Hydrochloride*

	Platelets per Cu.Mm.	Differential Platelet Formula (in Percentage)				Diagnosis
		Group 1	Group 2	Group 3	Group 4	
Before injection	445,000	26.0	61.5	8.0	3.5	Normal
After injection	604,000	21.9	70.1	8.0	0	
Before injection	252,000	25.0	55.0	18.0	2.0	Bronchial asthma
After injection	407,000	27.8	46.7	22.9	2.6	(during seizure)
Before injection	70,000	33.3	61.3	5.4	0	Chronic thrombocytopenic
After injection	120,000	26.0	62.5	11.5	0	purpura
Before injection	179,000	63.0	34.0	3.0	0	Aleukemic lymphatic
After injection	220,000	56.0	43.0	1.0	0	leukemia
Before injection	252,000	32.8	50.4	16.8	0	Aleukemic myelogenous
After injection	518,000	24.6	59.2	16.2	0	leukemia
Before injection	402,000	61.8	35.2	3.0	0	Catarrhal jaundice
After injection	575,000	28.5	68.0	3.0	0.5	

young erythrocytes. These observations on the effect of epinephrine, therefore, corroborate the view that the larger platelets represent more mature thrombocytes.

SUMMARY AND CONCLUSIONS

A method for studying the morphologic picture of the platelets in fresh wet preparations is described. It permits a simultaneous enumeration of the total thrombocyte content.

The behavior of the total and differential platelet counts in a number of important clinical conditions is presented and the significance of the deviations from the normal discussed.

92. Levy, R.: Zur Operation grosser Milztumoren, Arch. f. klin. Chir. **170**: 188, 1932.

93. Lampson, P. D.: The Role of the Liver in Acute Polycythemia: A Mechanism for the Regulation of the Red Corpuscle Content of the Blood, J. Pharmacol. & Exper. Therap. **7**:169 (July) 1915.

The normal platelets can be differentiated into four groups according to size: group 1, consisting of platelets 1.8 microns in diameter; group 2, consisting of platelets 2.5 microns in diameter; group 3, consisting of platelets 3.6 microns or more in diameter, and group 4, consisting of irregular-shaped platelets. In normal persons 18.6 per cent of all the circulating platelets belong to group 1, 63.3 per cent to group 2, 17.4 per cent to group 3 and 0.7 per cent to group 4.

In conditions associated with thrombocytosis and at times in those associated with thrombopenia, the deviation from the normal in the differential platelet formula is usually due to an absolute or relative increase in the number of small platelets, i. e., those belonging to group 1. The presence of increased numbers of the larger types of platelets is often associated with intense regenerative activity, abnormal function or hypoplasia of the megakaryocytes in the bone marrow.

Normally functioning platelets are usually normal morphologically. Functionally, the smaller platelets are much more active than the larger types. The small juvenile platelets possess high agglutinating powers, and their presence in large numbers constitutes a significant factor in the causation of spontaneous thrombosis in conditions associated with thrombocytosis.

Progress in Internal Medicine

BLOOD

A REVIEW OF THE RECENT LITERATURE

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In selecting articles to include in this second review of hematology, it has been the policy to consider only those which have a bearing on the recent advances in this field. It has not been possible, nor would it be advantageous, to present a summary of all papers which have been written during the year ending Jan. 1, 1935. If any essential articles have been omitted, we present our apologies. As a result of this plan, it may appear as though too much space has been devoted to some phases of the subject and too small amounts to others, but under the circumstances this could not be avoided.

PERNICIOUS ANEMIA

ETIOLOGY

The most important discussions centering about the etiology of pernicious anemia during the past year are primarily concerned with the nature of the intrinsic and the extrinsic factor, the site of the interaction between the two and the relation between them, and the etiology not only of pernicious anemia but also of some related conditions, such as sprue and the tropical macrocytic anemias.

Castle,[1] in his lecture before the Harvey Society, gave an excellent résumé of the knowledge concerning the present views in regard to the cause of pernicious anemia and included a list of the more important recent articles dealing with this topic and with related macrocytic anemias. He reiterated his former theory that addisonian pernicious anemia is due to a lack of the gastric factor in the stomach. Goldhamer and

From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan.

1. Castle, W. B.: The Etiology of Pernicious and Related Macrocytic Anemias, Science **82**:159, 1935.

his associates [2] expressed the belief that the change may be relative rather than absolute.

The nature of the intrinsic factor is still undetermined, although, according to Castle, it is known not to be hydrochloric acid or any of the recognized ferments of the gastric secretion. According to him it is thermolabile, as it is destroyed by heating for one-half hour at from 70 to 80 C. It is not present in the saliva or in the duodenal contents.

Castle also stated that the nature of the extrinsic factor is likewise unknown, although it has a wide distribution, for it is known to be present in beef muscle, eggs, autolyzed yeast, rice polishings, wheat germ and liver. This substance is thermostable, as it is not destroyed in autolyzed yeast when subjected to an autoclave pressure of 15 pounds (6.8 Kg.) for five hours.

Efforts have been made to ascertain the site of the interaction between the food and the gastric factors, but complete information concerning this is still lacking. Castle has not been able to form a thermostable substance similar to that found in liver by the incubation of beef muscle and normal gastric secretions in vitro. He has also been unable to determine to his satisfaction if the two factors, when incubated and then administered parenterally, can produce an effect which is comparable to that obtained by the oral administration of a material which is potent against pernicious anemia. According to him, confusing results may be obtained because the parenteral administration of substances containing proteins or their derivatives may produce a reticulocyte response which is not necessarily associated with an increase in the total red blood cell count or with clinical improvement of the patient.

In explaining the occasional response of a patient with pernicious anemia to large doses of the extrinsic factor alone, in the form of autolyzed yeast, he expressed the belief that it is associated with a spontaneous increase in the amount of intrinsic factor in the gastric secretions.

Miller and Rhoads [3] have contributed an experimental study dealing with the cause of the macrocytic anemias which may have an important bearing on the theories concerning these conditions. They considered that previously there has been no reported instance in which the major pathologic and physiologic changes of pernicious anemia have been

2. Goldhamer, S. M.; Isaacs, R., and Sturgis, C. C.: The Quantitative Relaship Between the Amount of the "Intrinsic Factor of Castle" and the Maturation of Red Blood Cells in Patients with Pernicious Anemia, J. Clin. Investigation **14**: 708, 1935.

3. Miller, D. K., and Rhoads, C. P.: The Experimental Production of Loss of Hematopoietic Elements of the Gastric Secretion and of the Liver in Swine with Achlorhydria and Anemia, J. Clin. Investigation **14**:153, 1935.

produced as a disease syndrome in a lower animal. By feeding to swine a modification of a diet that produces black tongue in dogs, they have produced a condition characterized by hematologic, lingual and gastrointestinal changes which are similar to those seen in cases of pernicious anemia. This diet was given to 15 animals, and macrocytic anemia developed in 9; of these, 7 were found to have achlorhydria, whereas hydrochloric acid had been present in the gastric secretions before the experiment. Lesions of the lingual, buccal or pharyngeal mucous membranes developed in all 9. It was also demonstrated by the method of Castle that there was a loss of the intrinsic factor in the gastric secretions. Furthermore, when extracts were prepared from the livers of these animals and given to patients with pernicious anemia, it was found that they did not contain the antianemic substance. A number of their animals, which were subjected to the same experimental procedures, were found to have microcytic anemia, which is somewhat difficult to explain. The general similarity, however, between the disease thus produced in swine and pernicious anemia, sprue and tropical anemia was impressive. It suggested to these observers that these conditions are due to a common cause which may be the result of the lack of intake of, or an inability to utilize, some poorly defined dietary constituent. While there may be some objections to this rather broad statement, it must be admitted that a disease has been produced experimentally in animals which simulates pernicious anemia in many respects.

Observations which can be correlated with those just cited have been made by Goodman, Geiger and Claiborn.[4] They determined the amount of the antianemic factor in the livers of swine after gastrectomy had been performed for periods varying from two to six months. An extract was prepared from the livers of these animals and given orally to patients with pernicious anemia. They concluded that the antianemic potency was diminished and that this may be detected as early as the third month after gastrectomy.

Meulengracht[5] and his collaborators have directed their attention toward localizing the area of the stomach which secretes the antianemic factor and determining if it is also present in the duodenum. It was first found that the glands of the cardiac, fundic and pyloric regions were anatomically distinct in swine. By careful dissection of the

4. Goodman, L.; Geiger, A. J., and Claiborn, L. N.: Anti-Anemia Potency of Liver After Gastrectomy in Swine, Proc. Soc. Exper. Biol. & Med. **32**:810, 1935.

5. Meulengracht, E.: Continued Investigations on the Presence of the Anti-Anaemic Factor in Preparations of Dried Stomach Substance from the Cardia, Fundus and Pylorus Regions: IV. Preparations from the Cardia Region, Acta med. Scandinav. **85**:50, 1935; V. Preparations from the Duodenum, ibid. **85**: 79, 1935.

stomachs of pigs and the administration of the material obtained to patients with pernicious anemia, it was found that the material containing glands of the fundus was inactive whereas that from the pyloric region was exceedingly potent. Tissue from the cardiac region of the stomach, while anatomically similar to that from the pyloric region, had only a slight potency. This was attributed to the sparsity of the glands in this area. It was also determined that the glands of Brunner in the duodenum had the same activity as those of the pylorus. It was suggested that the duodenal glands may assume the function of the glands of the pylorus in man when gastric atrophy develops or when the pylorus is resected. A theory is thus provided to explain why pernicious anemia does not develop under the aforementioned clinical conditions.

Jones, Benedict and Hampton [6] studied the gastric mucosa in 5 cases of pernicious anemia before and after treatment by gastroscopic and roentgenologic examinations, by direct observation at laparotomy and by histologic examination of biopsy material. Contrary to most observers, these investigators found that atrophy of the mucosa was not an invariable accompaniment of the disease, although it occurred, particularly during a relapse. After specific therapy, evidence of atrophy or hypertrophy tended to disappear. This was interpreted as an epithelial change rather than the healing of a chronic inflammatory process. The apparent return to normal from a grossly hypertrophic condition represents a subsidence of a chronic gastritis.

Wakerlin [7] reported the presence of an antianemic principle in normal human urine. This material, when injected into pigeons, increases the reticular material in the red blood cells in a manner similar to that observed after the use of the antianemic material present in liver. Wakerlin prepared an extract from urine by a procedure similar to that employed in making liver extracts for parenteral administration. This was given intramuscularly to a patient with pernicious anemia, and after thirty-five days of treatment the number of red blood cells had increased from 2,650,000 to 3,640,000 per cubic millimeter and the hemoglobin content from 63 to 83 per cent. These higher levels had not been obtained when liver therapy had been given to the same patient on a previous admission. Additional observations are necessary before definite conclusions can be made concerning the experiment.

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6. Jones, C. M.; Benedict, E. B., and Hampton, A. O.: Variations in Gastric Mucosa in Pernicious Anemia: Gastroscopic, Surgical and Roentgenologic Observations, Am. J. M. Sc. **190**:596, 1935.

7. Wakerlin, G. E.: Presence of Anti-Pernicious Anemia Principle in Normal Human Urine, Proc. Soc. Exper. Biol. & Med. **32**:1607, 1935.

Diagnosis.—Minot [8] discussed some aspects of the diagnosis of pernicious anemia which should be emphasized to all practitioners of medicine. He first deplored the fact that so much has been written about therapy during the past eight years that the need of a correct diagnosis has not received the proper attention. In not a few instances both liver and iron preparations are prescribed for a patient with anemia; improvement results, but the physician may never determine which one of these essential drugs are indicated. One hundred cases were studied to determine the relative frequency of the initial symptoms. It was found that in 33 per cent the initial symptom was weakness, in 31 per cent the symptoms were gastro-intestinal and in 26 per cent they were referred to the nervous system and in 10 per cent to the heart. The diagnosis of pernicious anemia was not established in the group until an average of one and three-tenths years after the initial symptoms occurred. In those patients whose earliest symptom was weakness or was cardiac, the diagnosis was recognized earlier than in those with gastro-intestinal or neural symptoms. While the gastro-intestinal or nervous manifestations may be mild, they may be present a long time before anemia is apparent, and it is not until the latter develops that the correct diagnosis is recognized.

Minot also emphasized the fact that there is frequently a history of vague gastro-intestinal symptoms of long standing in patients with pernicious anemia which can be attributed in part to gastric achlorhydria or to manifestations of the "deficient state." Furthermore, symptoms which suggest dysfunction of the gallbladder are not uncommon, and if they persist after proper treatment, it is additional evidence that they are dependent on disease of the gallbladder.

Mention is also made in Minot's article that the excess pigment metabolism which results in the lemon yellow color of the patient and also splenomegaly are now uncommon as compared to their previous incidence. The comparative rarity of both these conditions may possibly be due to the fact that modern treatment causes the anemia to disappear promptly, and as a result the excess pigment metabolism persists for only a short time. Certain concomitant conditions, such as cancer of the stomach, cirrhosis of the liver, myxedema and diabetes, are not rare in patients with pernicious anemia and should not cause the latter condition to be overlooked. It should be recognized that infections, an inadequate diet and possibly other factors may be the precipitating cause of pernicious anemia.

GASTRIC JUICE

Since Castle demonstrated the presence of the "intrinsic" factor in the gastric juice, the study of this secretion has become of increasing

8. Minot, G. R.: Some Aspects of the Diagnosis of Pernicious Anemia, M. Clin. North America **18**:935, 1935.

importance. Excellent reviews of the literature concerning gastric juice up to 1935 have been published.[9] It is now generally accepted that pernicious anemia is associated with achlorhydria, and it has been shown that the intrinsic factor is present in decreased amounts in the gastric juice of patients with pernicious anemia.

Several interesting experiments have been performed with gastric juice. Two groups of investigators working independently have noted the increased potency of liver extract by incubation with normal human gastric secretion.[10] On the basis of the theory that a hematopoiesis-stimulating substance is formed from the interaction of the extrinsic and the intrinsic factor and stored in the liver, it has been demonstrated that by removal of the stomach in swine the antianemic potency of the liver is gradually diminished.[4] The effectiveness of gastric juice injected intramuscularly in cases of pernicious anemia has been confirmed again.[11] A simple animal test to determine the presence or absence of the intrinsic factor in gastric secretion has been devised.[12] When normal gastric juice is filtered and neutralized with sodium bicarbonate and injected into white rats maintained on a milk and bread diet, a reticulocyte response is noted on from the third to the fifth day. Heated gastric secretion obtained from patients with pernicious anemia and that obtained from dogs are ineffective. The experiments with the secretion from dogs confirmed the contention that powdered dog stomach is of no value in the treatment of pernicious anemia. The gastric contents of patients with chronic microcytic anemia was effective.

The nature of the intrinsic factor is thought by some to be an enzyme and by others to be a hormone. The latter view, propounded by Morris, has recently been emphasized.[13]

9. Friedenwald, J.; Morrison, T. H., and Morrison, S.: Modern Conception Concerning Certain Gastric Affections: Disturbances of the Gastric Secretion and the Production of Various Types of Anemia and Certain Other Affections, Internat. M. Digest **26**:53, 1935. Klumpp, T. S., and Koletsky, S.: Relation of Gastric Secretion to Hematopoiesis, Ann. Int. Med. **8**:991, 1935.

10. (*a*) Fouts, P. J.; Helmer, O. M., and Zerfas, L. G.: Quantitative Studies on Increased Potency of Liver Extract by Incubation with Normal Human Gastric Juice, Ann. Int. Med. **8**:790, 1935. (*b*) Reimann, F.; Breuer, A., and Langecker, H.: Ueber die Wirksamkeitssteigerung der Leber nach Behandlung mit tierischem Magen, Magenschleimhaut und Extrakt aus Magenschleimhaut (künstlichen Magensaft): Untersuchungen zur Leberwirkung bei der Anaemia perniciosa, Ztschr. f. klin. Med. **127**:438, 1934.

11. Tochowicz, L.: Ueber den therapeutischen Wirkungsmechanismus des parenteral eingeführten, verdichteten, normalen Magensaftes (Addisin) im Verlaufe der Biermerschen Krankheit, Folia haemat. **53**:16, 1934.

12. Singer, Karl: Ueber eine tierexperimentelle Methode zum Nachweis des Castle-Prinzips des Magensaftes und deren klinische Bedeutung, Klin. Wchnschr. **14**:200, 1935.

13. Braun, B.: Der Mechanismus der therapeutischen Einwirkung des Castleschen Prinzips bei der perniziösen Anämie, Folia haemat. **53**:27, 1934.

Studies have been made of the gastric juice of children [14] and of adults [15] with types of anemia other than pernicious anemia. According to Ogilvie, the constituents of the gastric secretion with the exception of free and total acid, are normal in children with anemia. Defective secretion of hydrochloric acid and anemia appear to be closely related. Fouts and his co-workers found no alteration in the gastric juice of adults with anemia resulting from chronic hemorrhage. In cases of idiopathic hypochromic anemia, anemia associated with pregnancy and endocrine dysfunctions, anemia due to dietary deficiency and anemia refractive to medication, both the enzyme content and the acidity are reduced. The most consistent decreases in the enzyme content and acidity are seen in cases of idiopathic hypochromic anemia. These authors expressed the belief that if anacidity is present and enzymes are absent, the condition is permanent.

A few years ago Morris postulated that polycythemia was the result of overstimulation of hematopoietic activity by increased secretion of addisin. He advised constant gastric drainage with removal of the excess amount of the hormone as treatment for this condition. The experiments of Morris have been repeated by Briggs and Oerting,[16] who expressed the opinion that this type of therapy is most effective in cases of polycythaemia vera.

MANIFESTATIONS DUE TO LESIONS IN THE SPINAL CORD AND BRAIN

Although the symptoms and signs referable to degeneration of the spinal cord are regarded as a part of the disease process, involvement of the brain with its associated mental symptoms is not necessarily considered as a part of pernicious anemia.[17] The etiology of the changes in the nervous system remains obscure. It is believed by some, as a result of experimental evidence, that the manifestations in the spinal cord may result from a vitamin deficiency which is chronic rather than acute. [18] Others still maintain that there is a specific neurotoxin due

14. Ogilvie, J. W.: The Gastric Secretion in Anaemia, Arch. Dis. Childhood **10**:143, 1935.

15. Fouts, P. J.; Helmer, O. M., and Zerfas, L. G.: Gastro-Intestinal Studies: Gastric Juice in Anemias Other Than Pernicious Anemia, Am. J. Digest. Dis. & Nutrition **1**:677, 1934.

16. Briggs, J. F., and Oerting, H.: Influence of Gastric Lavage on Familial and Non-Familial Erythremia, Minnesota Med. **18**:499, 1935.

17. Osgood, C. W.: Mental Changes Associated with Pernicious Anemia, J. A. M. A. **104**:2155 (June 15) 1935. Preu, P. W., and Geiger A. J.: Symptomatic Psychoses in Pernicious Anemia, Ann. Int. Med. **9**:766, 1935.

18. Gildea, M. C. L.; Castle, W. B.; Gildea, E. F., and Cobb, S.: Neuropathology of Experimental Vitamin Deficiency: Report of Four Series of Dogs Maintained on Diets Deficient in B Vitamine, Am. J. Path. **11**:669, 1935.

to a disturbance in lipid metabolism or that the changes in the central nervous system are related to the anemia. Opposition to the latter view has been brought forward by observers who concluded from their research work with gastric juice that anemia and the changes in the spinal cord may occur together but that they are independent diseases.[19]

Involvement of the spinal cord has been reported in as high as 90 per cent of the cases of pernicious anemia, and the general consensus is that more than 70 per cent of patients with this condition exhibit neurologic manifestations. Manifestations of cerebral involvement have been noted in approximately 60 per cent of the persons suffering from pernicious anemia. The incidence of involvement of the central nervous system appears to be increasing since the advent of antianemic therapy.

The most common neurologic symptoms are numbness and tingling of the extremities, coldness, ataxia, loss of finer coordination of the fingers and disturbances of the bladder. The character of the signs depends on whether the changes in the posterior or in the lateral columns of the spinal cord predominate. The reflexes may be increased, decreased or lost. Disturbance in the vibratory sensation is the outstanding sign. There does not appear to be any specific mental picture,[20] and, as stated before, it is the opinion of some authors that the manifestations of cerebral involvement are independent of the disease process of pernicious anemia.

Conclusions drawn from the benefits of therapy must be guarded, as it is known that there may be spontaneous variations in the intensity of the neurologic manifestations without treatment. Improvement in symptoms and objective arrest in signs have been reported with the administration of liver, parenteral liver extract,[21] desiccated stomach, brain substance and iron, the use of a diet high in vitamins, removal of foci of infection and reeducation.[22] Manifestations referable to the

19. Salus, F., and Reimann, F.: Das Castlesche Ferment und die funikuläre Spinalerkrankung: Ein Beitrag zur Pathogenese des nervösen Krankheitssyndroms. (VI. Untersuchungen zur Leberwirkung bei der Anaemia perniciosa), Klin. Wchnschr. **13**:986, 1934.

20. Bowman, K. M.: Psychoses with Pernicious Anemia, Am. J. Psychiat. **92**: 371, 1935.

21. (*a*) Strauss, M. B.; Solomon, P.; Schneider, A. J., and Patek, A. J., Jr.: Subacute Combined Degeneration of the Spinal Cord in Pernicious Anemia: The Complete Arrest of the Lesion with Parenteral Liver Therapy, J. A. M. A. **104**: 1587 (May 4) 1935. (*b*) Sanford, C. H.: Pernicious Anemia with Normal Blood Picture, Ann. Int. Med. **9**:189, 1935. (*c*) Farquharson, R. F.: The Importance of Rest and Liver Therapy in the Treatment of Subacute Combined Degeneration of the Cord, Canad. M. A. J. **33**:473, 1935.

22. (*a*) Brain, W. R.: Subacute Combined Degeneration, Brit. M. J. **2**:1056, 1935. (*b*) Cohen, H.: Subacute Combined Degeneration of the Spinal Cord, Lancet **1**:1291, 1935.

posterior columns respond more readily than those due to lesions of the lateral columns. It is also to be noted that improvement may not be expected for several months after intensive therapy has been instituted. It is claimed that better results are obtained in younger persons [22b] and in those patients in whom the involvement of the central nervous system has been of short duration.[21c] If the cerebral changes are a result of the disease process, some improvement may be anticipated; however, if a psychosis exists independent of pernicious anemia, no improvement can be expected with antianemic therapy.

BLOOD

Emerson and Helmer [23] found that the condition of acid-base equilibrium in 29 patients with pernicious anemia was independent of the clinical status. There was an apparent tendency toward alkalosis, but the authors considered the acid-base equilibrium as normal. The p_H varied over a range twice as broad as in normal persons. The daily administration of hydrochloric acid produced no appreciable change in the acid-base equilibrium of the blood in patients with pernicious anemia.

Watson [24] isolated coproporphyrin I from the feces of 2 patients with pernicious anemia. After liver therapy, the amount was significantly decreased to the amount found in normal persons and in patients with other types of anemia.

The color index of serum, as determined by Schmehle and Schmid [25] with the step photometer, was increased in cases of severe pernicious anemia but decreased rapidly after therapy. Relapse is less likely to occur in patients whose color index is normal than in those in whom the index remains high in spite of normal erythrocyte values. Pernicious anemia is contrasted to "achylic anemia," in which the index value is subnormal.

Wintrobe and Shumacker [26] called attention to certain similarities between the blood of the fetus and that of patients with pernicious anemia in whom an induced remission has been instituted with potent therapy. In the fetus there is macrocytosis; reticulocytosis and nucleated

23. Emerson, C. P., Jr., and Helmer, O. M.: Reaction (p_H) and Carbon Dioxide Content of Venous Plasma in Pernicious Anemia, Arch. Int. Med. **55**: 254 (Feb.) 1935.

24. Watson, C. J.: Concerning Naturally Occurring Porphyrins: Isolation of Coproporphyrin I from Feces of Untreated Cases of Pernicious Anemia, J. Clin. Investigation **14**:116, 1935.

25. Schmehle, E., and Schmid, H.: Ueber Serumfarbkurven bei perniziöser und einfach achylischer Anämie, Klin. Wchnschr. **14**:675, 1935.

26. Wintrobe, M. M., and Shumacker, H. B., Jr.: Comparisons of Hematopoiesis in Fetus and During Recovery from Pernicious Anemia, Together with Consideration of Relationship of Fetal Hematopoiesis to Macrocytic Anemia of Pregnancy and Anemia in Infants, J. Clin. Investigation **14**:837, 1935.

red blood cells appear in the peripheral circulation. As the time of birth approaches, the blood assumes more of the adult characteristics.

In the bone marrow of the sternum, Isaacs [27] found no simple correlation between the total number of nucleated cells of all types and the peripheral red blood cell count. There was considerable variation in the cellularity of the marrow in different persons. The blood count of 3,000,000 red blood cells per cubic millimeter indicates the point at which the megaloblastic marrow approaches the normal condition. It is at this point that some patients become resistant to specific therapy.

Sanford [21b] emphasized the fact that the blood may be normal in a patient with pernicious anemia, with the involvement limited to the central nervous system. He reported 3 cases in which the response to liver extract was good.

Minot and Castle [28] made an excellent summary of the present knowledge of the behavior of reticulocytes in cases of pernicious anemia in which remissions were induced. In considering the reticulocyte responses to medication, it is important to evaluate the nonspecific or "irritant" effects of certain substances, such as potassium arsenite.

Murphy [29] warned against one placing too great emphasis on comparable reticulocyte responses, as he considered that some substances may cause an increase in the reticulocyte count, whereas others may not produce this effect although they possess the ability to increase the erythrocyte count.

TREATMENT

Wilkinson [30] again emphasized the necessity for the permanent use in cases of pernicious anemia of adequate amounts of a potent stomach or liver preparation. In cases in which there were neurologic symptoms he recommended full doses without a decrease. The prognosis of uncomplicated pernicious anemia is good if these points are observed.

The question of an increase in the potency of kidney and liver after autolysis was reinvestigated by Castle and Strauss,[31] who concluded

27. Isaacs, R.: Bone Marrow Changes (Quantitative) in Patients with Pernicious Anemia During Period of "Reticulocyte" Response, Tr. A. Am. Physicians **50**:249, 1935.

28. Minot, G. R., and Castle, W. B.: Interpretation of Reticulocyte Reactions: Their Value in Determining Potency of Therapeutic Materials, Especially in Pernicious Anemia, Lancet **2**:319, 1935. Minot, G. R.: Interpretation of Reticulocyte Responses in Pernicious Anemia, Tr. A. Am. Physicians **49**:287, 1934.

29. Murphy, W. P.: Facts Concerning Treatment of Anemia, New York State J. Med. **35**:973, 1935.

30. Wilkinson, J. F.: Treatment of Pernicious Anemia, Practitioner **134**: 272, 1935.

31. Castle, W. B., and Strauss, M. B.: Effect of Autolysis on Potency of Liver in Treatment of Pernicious Anemia, J. A. M. A. **104**:798 (March 9) 1935.

that the autolyzed liver has less potency than the amounts of material from which it was derived. Conner and McQuiston [32] reported good responses in 3 patients, poor responses in 3 and doubtful but apparently poor responses in 2.

The dietary factor active against pernicious anemia (extrinsic factor of Castle) was found to be present in the white of egg by Miller and Rhoads.[33] While this is compatible with the concept that the extrinsic factor is vitamin B_2 (G), it does not prove it, as white of egg contains many other substances.

Mogensen [34] pointed out that there is a form of pernicious anemia in which there is a deficiency of iron and in which large doses of iron preparations are a necessary supplement to treatment with liver or stomach preparations when the latter are inadequate to produce a complete remission. Sherman and his co-workers [35] confirmed the experiences of other authors in that the feeding of liver alone, without the addition of meat, fruit or vegetables, is effective. They recommended smaller doses than have been used (from 150 to 200 Gm. daily). Their experience with powdered liver extract was not good. After from three to four months of treatment, the urobilin in the urine, the blood sugar content and the ability to digest neutral fat and muscle tissue approached normal. They noted improvement in the symptoms referable to the spinal cord after an uninterrupted liver diet.

Scowen and Spence [36] used a concentrated liver extract intramuscularly, from 5 to 10 cc. being required to bring about a complete remission. As with other preparations, they found that the interval between maintenance doses varies from patient to patient and in the same patient from time to time.

Decastello [37] found that he could produce hematopoietic improvement in patients by giving a daily enema of 300 cc. of urine of healthy persons or of patients with pernicious anemia. Urine from patients with other forms of anemia was ineffective. Decastello considered that the active

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32. Conner, H. M., and McQuiston, J. S.: Autolyzed Liver in Treatment of Pernicious Anemia, Proc. Staff Meet., Mayo Clin. **10**:740, 1935.

33. Miller, D. K., and Rhoads, C. P.: Reticulocyte Response in Guinea Pigs Following Oral Administration of Certain Anti-Anemic Substances, New England J. Med. **213**:99, 1935.

34. Mogensen, E.: Iron Treatment in Pernicious Anemia, Ugesk. f. læger **96**: 1368, 1934.

35. Sherman, S. I.; Semenova, M. P.; Alekseev-Berkman, I. A.; Shcheglova, A. V., and Shatalova, A. A.: Dietetic Treatment of Pernicious Anemia, Sovet. vrach. gaz., Feb. 28, 1935, p. 295.

36. Scowen, E. F., and Spence, A. W.: Concentrated Liver Extract for Parenteral Administration in Pernicious Anaemia, Brit. M. J. **1**:246, 1935.

37. Decastello, A.: Ueber antianämisch wirksame Substanzen im Harn, Med. Klin. **31**:377, 1935.

substance in urine was the same as the "intrinsic factor" of Castle and that it may be present in the blood of patients with pernicious anemia but is not secreted in their stomachs.

Wakerlin [7] made a urine concentrate from normal persons and found that it had some hematopoietic effect.

Strauss and his co-workers [21a] were able to arrest the progress of the neurologic lesions in 26 patients with pernicious anemia and to prevent their development in 84 other patients by adequate treatment with liver extract intramuscularly. In contrast to this, Straube [38] presented evidence based on a study of his patients which makes him conclude that the neurologic symptoms seen in cases of pernicious anemia cannot be cured or prevented.

Tochowicz [11] used concentrated gastric juice (hog or human) and prepared a sterile acetone extract which he gave intramuscularly. A single injection produced a complete remission of all symptoms (except return of normal gastric secretion) for several months. Braun [13] repeated Castle's experiments, using hog gastric juice in 1 patient and human secretion in another, with good responses.

Meulengracht [39] found that most of the antianemic property of hog stomach was in the pyloric glandular region. The duodenum also possessed powerful antianemic properties. The glands of Brunner in this region are similar, histologically, to those in the pyloric region of the stomach.

Schemensky [40] made an active preparation from dried defatted hog colon, which produced results similar to those produced by liver or stomach tissue, but they were obtained somewhat more slowly.

Ungley and James [41] found that yeast products given parenterally were not effective in the treatment of pernicious anemia, which supports

38. Straube, G.: Die Nervenstörungen der perniziösen Anämie unter besonderer Berücksichtigung ihrer Beeinflussbarkeit durch die Therapie, Med. Klin. **31**:1164, 1935.

39. Meulengracht, E.: Preliminary Report on Presence of Anti-Anemic Factor in Dried Stomach Preparations from Cardiac, Fundic and Pyloric Portion, Respectively, and from Duodenum: Preparations from Duodenum, Ugesk. f. læger **97**:725, 1935; Pyloric Glands in Relation to Pernicious Anemia, Nord. med. tidskr. **9**:865, 1935; The Glands of the Stomach in Relation to Pernicious Anemia, with Special Reference to the Glands in the Pyloric Region, Proc. Roy. Soc. Med. **28**:841, 1935; footnote 5.

40. Schemensky, W.: Zur Pathologie der perniziösen Anämie. Therapeutische Erfolge mit Verfütterung getrockneten Schweinedickdarmpulvers. Mit einem Anhang: Therapeutische Betrachtungen zur Colitis gravis, Ztschr. f. klin. Med. **128**:428, 1935.

41. Ungley, C. C., and James, G. V.: Effect of Yeast and Wheat Embryo in Anaemias: Nature of Haemopoietic Factor in Yeast Effective in Pernicious Anaemia, Quart. J. Med. **3**:523, 1934.

the contention that the hematopoietic substance in yeast is more like the extrinsic factor of Castle than liver extract. However, there was no parallel between the vitamin B_2 potency of the yeast extracts and the hematopoietic effects. The response to yeast or wheat germ given by mouth in 10 of 18 patients indicates that some patients retain to a degree the ability to secrete the intrinsic factor.

Mermod and Dock [42] produced lasting remissions in two patients with pernicious anemia by the intravenous injection of 1.5 per cent congo red 4 B in a 6 per cent solution of dextrose, from 60 to 90 cc. in from five to ten days. The authors considered the action as one of neutralization of toxic substances.

Dakin and West [43] isolated a hematopoietic material from liver which produced optimal results in doses of 80 mg. The method used by these investigators consists of removal of the inactive material with alcoholic calcium acetate and precipitation of the active material with Reinecke salt in acid solution. The material is salted out with ammonium sulfate and reprecipitated with magnesium sulfate, sodium chloride or flavianic acid. The yield is about 1 per cent of the dry liver extract powder. The material is inactivated by sodium hydroxide, sulfuric acid and salts of heavy metals. Deutsch and Wilkinson [44] found that the antianemic principle of liver extract was not the substance which caused the formation of methemoglobin in hemolyzed blood.

West [45] summarized the present knowledge concerning the chemical nature of the hematopoietically active substance in liver. According to him, the active material forms a precipitate with phosphotungstic acid and with Reinecke's salt. Salts of gold, silver, platinum and mercury, as well as sodium hydroxide and mineral acids, destroy the potency. Heating to 100 C. at p_H 5 does not lessen the clinical effect. It is soluble in water, and the partly purified material is soluble in slightly acid 95 per cent alcohol. It is insoluble in ether. The substance does not give a reaction to the biuret test; it contains carbon, hydrogen, oxygen and nitrogen. Phosphorus and sulfur are absent. Kyer [46] found that the active material could be purified by adsorption on charcoal from an acid solution.

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42. Mermod, C., and Dock, W.: Colloidal Dye Effective in Treating Pernicious Anemia and Evoking Reticulocytosis in Guinea Pigs, Science **82**:155, 1935.

43. Dakin, H. D., and West, R.: Observations on Chemical Nature of Hematopoietic Substance in Liver, J. Biol. Chem. **109**:489, 1935.

44. Deutsch, W., and Wilkinson, J. F.: "Methaemoglobin-Production" Test for Assaying Anti-Anemic Potencies of Liver Extracts, Brit. J. Exper. Path. **16**:33, 1935.

45. West, R.: Antianemic Material of Liver and Stomach, J. A. M. A. **105**: 432 (Aug. 10) 1935.

46. Kyer, J. L.: Charcoal Adsorption as a Method for the Preparation of a Concentrated Liver Extract, Proc. Soc. Exper. Biol. & Med. **32**:1102, 1935.

For assay of the material, Jacobson [47] injected it into selected guinea-pigs and studied the blood for a reticulocyte response. The responses were quantitative and were expressed in "guinea-pig units." The unit is "the minimal amount of material per kilogram guinea pig, which, after a single intraperitoneal administration, induces a positive reticulocyte response in at least two of three reactive guinea pigs." The phenomenon was confirmed by Miller and Rhoads.[33]

Muller [48] used pigeons to test the hematopoietic activity of liver extract. Injections of potent material caused an increase in the percentage of reticulocytes, but similar responses were obtained from intravenous injections of lysine and leucine, but argenine and histidine gave but indefinite responses. After the administration of liver extract the megaloblasts of the bone marrow were transformed into more adult red blood cells, but after the administration of lysine or leucine there were an increase and extension of erythroblastic tissue, with numerous megaloblasts and mitotic figures.

Kamerling,[49] testing Singer's method of evaluating the potency of the Castle principle generated by the action of gastric juice on meat or liver found that similar responses could be elicited by the injection into rats of mixtures of pepsin and hydrochloric acid.

Minot,[50] in the Nobel lecture, emphasized the necessity of giving sufficient potent material, enough to supply, besides the hematopoietic requirements, all the demands of the body for the substance and to fill it adequately with a reserve supply. It is probable that more material is required to improve or to inhibit the progress or development of neurologic symptoms than is necessary to maintain a normal blood count. Minot wisely added that "the physician, however, must do more for his patient than prescribe a proper amount of liver, stomach or the like; he should attend to all aspects of the case and not neglect attention to the individual's manifold problems of thought and action."

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47. Jacobson, B. M.: Response of Guinea Pig's Reticulocytes to Substances Effective in Pernicious Anemia: Biologic Assay of Therapeutic Potency of Liver Extracts, J. Clin. Investigation **14**:665, 1935; Assay on Guinea Pigs of Hematopoietic Activity of Human Livers, Normal and Pernicious Anemia, ibid. **14**:679, 1935.

48. Muller, Gulli Lindh: Reticulocyte Responses in the Pigeon Produced by Material Effective and Non-Effective in Pernicious Anemia with Description of the Histologically Different Reactions of the Bone Marrow, New England J. Med. **213**:1221, 1935.

49. Kamerling, A. W. C. G.: Zur Frage der tierexperimentellen Methode Singers zum Nachweis des Castle-Prinzips, Wien. klin. Wchnschr. **48**:1140, 1935.

50. Minot, G. R.: Development of Liver Therapy in Pernicious Anemia, Lancet **1**:361, 1935.

Stare and Thompson [51] used a purified flavine made from liver in the treatment of patients with pernicious anemia. No hematopoietic response was noted when this was given intramuscularly. Conversion of the flavine of liver extract into photoflavine did not impair its potency.

Liver contains both the hematopoietically active substance and the material which can act as the "extrinsic factor" when acted on by gastric juice. Fouts, Helmer and Zerfas [10a] found that the potency of liver extract could also be increased by digestion with normal human gastric juice but that the final product was not as active as material derived from whole liver under these circumstances. To increase the potency of 4.5 Gm. of liver extract satisfactorily, 50 cc. or more of gastric juice was necessary.

Goldhamer, Isaacs and Sturgis [2] found that patients with pernicious anemia secreted the intrinsic factor of Castle during relapse, but in greatly diminished quantity. The average total secretion in these patients was only 20 cc. per hour as compared with 150 cc. in normal persons under the same conditions. Gastric secretion collected from patients with pernicious anemia when used in sufficient amounts and incubated with meat caused an induced remission in 2 patients with pernicious anemia. A third patient responded to intramuscular injections of his own gastric juice.

MACROCYTIC ANEMIA OTHER THAN PERNICIOUS ANEMIA

In several recent reviews [52] it has been pointed out that macrocytic anemia may be produced by many different factors. It is generally accepted that the interaction of the extrinsic and the intrinsic factor produces a substance necessary for the normal development of red blood cells. The product formed is absorbed from the intestine, stored in the liver and released to the body tissues for utilization as needed. Macrocytic anemia will be produced if there is a disturbance of any of the factors which are involved in this mechanism.

The value of food as a satisfactory source of the extrinsic factor for the treatment of macrocytic anemia due to deficiency has been demonstrated clinically [53] and experimentally.[54] Although the stomach

51. Stare, F. J., and Thompson, L. D.: Hepatoflavin and Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **33**:64, 1935.

52. Sturgis, C. C.; Isaacs, Raphael; Goldhamer, S. M.; Bethell, F. H., and Farrar, G. E., Jr.: Blood, Arch. Int. Med. **55**:1001 (June) 1935. Vaughan, J. M.: Anaemias Due to a Deficiency of the Principle in Liver, Which Is Effective in the Treatment of Addisonian Pernicious Anemia, Proc. Roy. Soc. Med. **28**:475, 1935. Castle.[1]

53. (*a*) Castle, W. B.; Rhoads, C. P.; Lawson, H. A., and Payne, G. C.: Etiology and Treatment of Sprue: Observations on Patients in Puerto Rico and

(Footnotes continued on next page)

tissue is the source of the intrinsic factor, gastrectomy usually results in microcytic rather than macrocytic anemia.[55] The same results have been observed by other investigators.[56] Apparently other nutritional factors, such as minerals and vitamins, and their effects on the body tissues are important in the production of secondary anemia. The microcytic anemia produced in animals is also explained by the fact that there is a constitutional difference between man and animals. It has been demonstrated that desiccated dog stomach is inactive or less than one-half as potent as hog stomach and that dog liver is less effective than calf liver.[56a]

Obstruction of the small intestine,[57] infestation with a tapeworm,[58] celiac disease, gastrocolic fistula and sprue [53] have all been observed in association with macrocytic anemia. Study of the bone marrow in some cases of sprue, during relapse and during remission, revealed a striking similarity to the pathologic changes observed in pernicious anemia.[53a]

It has recently been demonstrated that experimental cirrhosis is associated with macrocytic anemia.[59] These observations tend to confirm the clinical reports of macrocytic anemia occurring in hepatic disease.[60] There appears to be sufficient evidence that the intrinsic

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Subsequent Experiments on Animals, Arch. Int. Med. **56**:627 (Oct.) 1935. (*b*) Snell, A. M.; Camp, J. D., and Watkins, C. H.: Nontropical Sprue (Chronic Idiopathic Steatorrhea), Proc. Staff Meet., Mayo Clin. **10**:177, 1935. (*c*) Fairley, N. H.: Tropical Sprue and Its Modern Treatment, Brit. M. J. **2**:1192, 1934.

54. Day, P. L.; Langston, W. C., and Shukers, C. F.: Leukopenia and Anemia in Monkey Resulting from Vitamin Deficiency, J. Nutrition **9**:637, 1935. Miller and Rhoads.[3]

55. Hartman, H. R., and Eusterman, G. B.: Anemia Following Operations on the Stomach, Am. J. Digest. Dis. & Nutrition **1**:829, 1935. Hunter, D.: New Aspects of Deficiencies in Nutrition, Lancet **1**:1025, 1935. Hartfall, S. J.: Gastrectomy and Gastro-Enterostomy Anemia, Guy's Hosp. Rep. **84**:448, 1934. Miller and Rhoads.[3]

56. (*a*) Ivy, A. C.; Richter, O.; Meyer, A. F., and Greengard, H.: The Relation of Gastrectomy to Anemia on the Presence of the Substances Effective in Pernicious Anemia in Canine Stomach and Liver, Am. J. Digest. Dis. & Nutrition **1**:116, 1934. (*b*) Dragstedt, C. A.; Bradley, J. D., and Mead, F. B.: Effect of Iron on Hemoglobin Regeneration in Gastrectomized Dogs, Proc. Soc. Exper. Biol. & Med. **33**:58, 1935.

57. Jonsson, E.: Des anémies qui, dans la tuberculose, rappellent l'anémie pernicieuse, Acta med. Scandinav. **83**:505, 1934.

58. Hunnicutt, T. N., Jr.: An Anemia Associated with a Fish Tapeworm (Diphyllobothrium Latum) Infestation, J. A. M. A. **104**:1984 (June 1) 1935.

59. Higgins, G. M., and Stasney, J.: Macrocytic Anemia in Experimental Cirrhosis, Proc. Staff Meet., Mayo Clin. **10**:429, 1935.

60. Malamos, B.: Das rote Blutbild bei Lebererkrankungen, Deutsches Arch. f. klin. Med. **177**:209, 1935. Wilkinson, J. F., and Israëls, M. C. G.: Achresthic Anaemia, Brit. M. J. **1**:139 and 194, 1935. Kersley, G. D.: Atypical Megalocytic Anaemia, ibid. **2**:994, 1935.

factor may be present in the stomach, but because of damage to the liver the hematopoietic substance cannot be stored and presented to the bone marrow for utilization, and as a result macrocytic anemia develops.

In addition to the foregoing factors concerned in the production of macrocytic anemia, other causes have been suggested.[61]

Treatment of the anemia associated with these various conditions depends on which factor or factors are contributing to the cause in each given instance. If the intrinsic or the extrinsic factor is absent, liver administered orally may be appropriate; however, if there is a disturbance of absorption or storage, the administration of liver parenterally should be instituted. A well balanced diet has also been recommended.

ANEMIA OF PREGNANCY

It is customary to classify in two types anemia directly attributable to the gravid state. The more prevalent is the hypochromic and microcytic anemia so often associated with a deficiency of iron. Of 51 pregnant women studied by Davies and Shelley,[62] 6 were found to have anemia of the hypochromic type. Achlorhydria or hypochlorhydria was found in all but 1 of the women. Schultz [63] emphasized that in anemia of pregnancy of the hypochromic type there are evidences of active regeneration of the blood, the condition tends to improve spontaneously after childbirth, and an especially important rôle in its production is the loss of blood whether by previous menorrhagia, abortion or childbirth. He found that after repeated pregnancies spontaneous recovery from this type of anemia is greatly prolonged. Simple iron preparations are effective against the hypochromic anemia of pregnancy, but the response to treatment is slower than in nonpregnant persons.[64]

Macrocytosis and hyperchromia characterize the second and much less common type of anemia of pregnancy. In addition to dietary deficiencies and defects of gastric secretion as causative factors in the development of anemia of the macrocytic or pernicious type, Wintrobe and Shumacker [26] suggested that the demands of fetal hematopoiesis may place an excessive drain on the maternal supply of the hepatic

61. Stern, R. O.: Achlorhydria in the Psychoses, with Special Reference to Coincident Anaemia, J. Ment. Sc. **81**:358, 1935. McGowan, J. P.: Pernicious Anaemia: Some Considerations in Regard to Its Nature and Pathogenesis, Edinburgh M. J. **42**:293, 1935. Keyes, H. R.: The Mycology of Sprue and Pernicious Anemia, Am. Med. **41**:9, 1935. Jonsson.[57]

62. Davies, D. T., and Shelley, U.: Some Observations on Hypochromic Anaemia and Its Relation to Pregnancy, Lancet **2**:1094, 1934.

63. Schultz, W.: Die essentielle hypochrome Anämie mit Berücksichtigung der essentiellen Schwangerschaftsanämie, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **47**:327, 1935.

64. Bethell, F. H.: The Application of Diagnostic Criteria to the Treatment of the Anemias, New York State J. Med. **35**:799, 1935.

principle essential for normal maturation of the erythrocytes. Strauss [65] found that adequate treatment of pernicious anemia of pregnancy requires the use of much larger doses of liver extract orally or parenterally than are needed in the management of the usual addisonian pernicious anemia. Ionesco and Bonciu [66] have obtained good results in the treatment of this form of anemia by the use of preliminary transfusions of blood followed by the administration of 250 Gm. of fresh cooked liver daily.

ANEMIA ASSOCIATED WITH OTHER DISEASE ENTITIES

HEMOLYTIC JAUNDICE

The behavior of the red blood cells after splenectomy was studied by Levi and Bairati.[67] The microcytosis tended to be replaced by a normocytosis, with a decrease in the number of reticulocytes, although some microcytes persisted and the resistance of the red blood cells to hypotonic solutions of sodium sulfate continued to be abnormal. The authors expressed the belief that the spheroidal microcytosis does not represent a constitutional defect of erythropoiesis but is secondary to hyperhemolysis.

In a study of bone marrow, Dameshek [68] found in 1 case that the ratio of red blood cells to white blood cells was 0.4:1, and the percentage of erythroblasts was 80 per cent; in another case the red blood cell-white blood cell ratio was 1:1, with an increase in the erythroblasts to 80 per cent. There was a definite increase in the number of histiocytes.

In a case described by Waugh,[69] marked improvement followed the use of liver extract intravenously. Smith [70] was able to trace the disease through four generations in a patient under his care. In Langston's [71]

65. Strauss, M. B.: The Etiology and Prevention of Anemia in Pregnancy, Ann. Int. Med. **9**:38, 1935.

66. Ionesco, V. T., and Bonciu, D.: Contribution à l'étude de l'anémie pernicieuse gravidique, Sang **9**:510, 1935.

67. Levi, G. M., and Bairati, A.: Distribution of Erythrocyte Population in Regard to Diameters and Osmotic Resistance in Splenectomized Cases of Hemolytic Icterus: Contribution to Understanding of Pathogenesis of Disease, Am. J. M. Sc. **190**:610, 1935.

68. Dameshek, W.: Biopsy of the Sternal Bone Marrow: Its Value in the Study of Diseases of Blood-Forming Organs, Am. J. M. Sc. **190**:617, 1935.

69. Waugh, T. R.: Pernicious Anemia in an Individual with Familial Hemolytic Jaundice, Folia haemat. **53**:291, 1935.

70. Smith, G. O.: Chronic Hereditary Hemolytic Jaundice, J. A. M. A. **105**: 1187 (Oct. 12) 1935.

71. Langston, W.: Hemolytic Icterus with Infantilism, South. M. J. **28**:316, 1935.

case hemolytic icterus was associated with infantilism. Splenectomy and hormone therapy were followed by a return to normal.

Doan, Curtis and Wiseman [72] noted an increase in the red blood cell count of a million or more immediately after splenectomy. Several factors appeared to play a part: disgorgement of the sequestered blood cells from the splenic reservoir and sudden elimination of the destructive activity of the splenic phagocytes and hyperactive hematopoiesis. The spleen is considered as the major pathologic agent in congenital hemolytic jaundice. Splenectomy is indicated as a prophylactic measure against clinical exacerbations of excessive hemolytic activity in the chronic and subacute manifestations of the disease as well as in acute hemoclastic crises, whether spontaneous or precipitated, and regardless of the severity of the anemia.

Heilmeyer [73] described hemolytic hypersplenia as a definite form of acquired hemolytic jaundice. In this condition there is a severe degree of hemolytic anemia, with reticulocytosis, microspherocytosis and splenic tumor. The condition is of sudden onset, there is no history of the disease in the family, and cure occurs after splenectomy. The author measured the red blood cells from the splenic artery and vein and found an increase in microspherocytosis in the latter. Severe infections and endocrine dyscrasias may be etiologic factors.

In hemolytic jaundice the plasma phosphatase is normal in amount, whereas in jaundice due to mechanical obstruction of the bile ducts the amount is increased. In toxic or infective disease of the liver the amount may be normal or elevated (Herbert [74]).

Daland and Worthley [75] studied the resistance of red blood cells to hemolysis in solutions of sodium chloride in a number of diseases. After splenectomy in hemolytic jaundice a temporary hypochromic blood picture may be accompanied by increased maximal resistance. Before splenectomy, decreased maximum resistance is the rule. Decreased minimal resistance is common in this disease; rarely is it normal.

Rozendaal, Comfort and Snell [76] concluded that an indirect van den Bergh reaction in serum containing bilirubin in amounts more than

72. Doan, C. A.; Curtis, G. M., and Wiseman, B. K.: Hemolytopoietic Equilibrium and Emergency Splenectomy, J. A. M. A. **105**:1567 (Nov. 16) 1935.

73. Heilmeyer, L.: Hämolytische Hypersplenie: Erworbener hämolytischer Ikterus, Deutsches Arch. f. klin. Med. **178**:89, 1935.

74. Herbert, Freda K.: Plasma Phosphatase in Various Types of Jaundice, Brit. J. Exper. Path. **16**:365, 1935.

75. Daland, G. A., and Worthley, K.: Resistance of Red Blood Cells to Hemolysis in Hypotonic Solutions of Sodium Chloride: Observations in Blood Disorders, J. Lab. & Clin. Med. **20**:1122, 1935.

76. Rozendaal, H. M.; Comfort, M. W., and Snell, A. M.: Slight and Latent Jaundice: The Significance of Elevated Concentrations of Bilirubin Giving an Indirect van den Bergh Reaction, J. A. M. A. **104**:374 (Feb. 2) 1935.

normal does not always mean hemolytic disease. In hemolytic anemia associated hepatic injury is almost universal.

Watson [77] isolated a new porphyrin from the feces of a patient during a hemolytic crisis. It occurred in association with a marked increase in coproporphyrin I.

For the congenital as opposed to the acquired (chemical or bacterial toxin) type of hemolytic jaundice, Lehndorff [78] based the diagnosis on icterus, pallor, splenomegaly, with microcytosis, reduced resistance of the red blood cells to hypotonic solutions of sodium chloride and increase in the number of reticulocytes. In children the icterus may be mild or absent, and pallor is not constant. The microcytosis is characteristic, the average corpuscular diameter being 5.8 microns instead of 7.8. The cells are spheroid rather than flat, and the average volume is greater than normal (100 cubic microns). The hemoglobin content of the red blood cell is relatively high, with a color index of 1 or above. The author considered that the anemia results from the attempt of the reticulo-endothelial system, especially the spleen, to remove the abnormally shaped (spheroid) red blood cells. Splenomegaly develops, and later icterus, if the liver cannot metabolize the excess pigment adequately. Transfusion of blood is recommended during the acute attack and occasionally treatment with liver and iron preparations. Splenectomy should be done only when the hemolytic crises are recurrent, but during the periods of remission no therapy is indicated.

APLASTIC ANEMIA

The literature contains reports of cases of aplastic types of anemia in association with abdominal lymphogranuloma, ankylostomiasis and arsphenamine, neoarsphenamine (Imrie [79]), benzene (Cabot,[80] case 21301) and acetarsone poisoning and also during the course of the treatment of tuberculosis with gold compounds (de Lavergne and Bichat [81]), and after radiotherapy (Marchal, Mallet, Soulié and Grupper [82]). There

77. Watson, C. J.: Concerning Naturally Occurring Porphyrins: Isolation of Hitherto Undescribed Porphyrin Occurring with Increased Amount of Coproporphyrin I in Feces of Case of Familial Hemolytic Jaundice, J. Clin. Investigation **14**:110, 1935.

78. Lehndorff, H.: Hämolytische Anämie—Die Kugelzellenkrankheit, Med. Klin. **31**:74, 1935.

79. Imrie, A. H.: Aplastic Anaemia Following Neokharsivan, Lancet **2**:73, 1935.

80. Aplastic Anemia (Benzol Poisoning), Cabot Case 21301, New England J. Med. **213**:182, 1935.

81. de Lavergne, V., and Bichat, J.: L'aleucie hémorragique accident de la chrysothérapie, Rev. méd. de l'est **63**:457, 1935.

82. Marchal, G.; Mallet, L.; Soulié, P., and Grupper, C.: Deux cas d'aleucie hémorragique post-radiothérapique, Sang **9**:766, 1935.

is considerable confusion in the literature concerning the use of the term aplastic anemia, some authors referring to a selective decrease in the number of red blood cells and others to a panmyelophthisis, whereas in several cases reference is made to aplastic anemia during the course of aleukemic leukemia. The treatment appears to be limited to the transfusion of blood. The administration of pentose nucleotide is not effective (Holmes [83]).

CANCER

The blood picture associated with cancer is neither pathognomonic nor constant, nor does the anemia associated with cancer give any indication of the site of the malignant process. The anemia may be macrocytic or microcytic, and the color index, high or low. Usually there is leukocytosis. The number of platelets in the blood may be increased, decreased or normal. The etiology of the anemia has been discussed by many investigators,[84] who have offered several explanations. If there is a disturbance in iron metabolism (failure of absorption or chronic hemorrhage), microcytic anemia results. Secondary anemia is also attributed to a toxic effect on the bone marrow or to hemolysis. Macrocytic anemia associated with cancer of the stomach may result from an insufficiency or lack of secretion of the "active" principle by the cancerous gastric mucosa,[85] from metastasis to the bone marrow or from the coincidental existence of pernicious anemia and cancer. In view of the relationship of macrocytic anemia and cancer of the stomach, it has been suggested that routine roentgenograms of the gastro-intestinal tract be made.[84d] The treatment of the anemia depends on the etiology, and though it may be aided by proper diet, large doses of iron and antianemic therapy, it cannot be eliminated without removal of the primary causal factor.

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83. Holmes, J. M.: Aplastic Anemia: Two Fatal Cases Treated by Blood Transfusion and Pentose Nucleotide, Lancet **2**:71, 1935.

84. (*a*) Labbe, M., and Balmus: Anémie pernicieuse et cancer de l'estomac, Sang **9**:113, 1935. (*b*) Miller, T. G.: Addisonian Anemia and Carcinoma of the Stomach in the Same Individual: Report of Three Cases; Chronic Gastritis as Probable Basis for Both Diseases, Internat. Clin. **1**:167, 1935. (*c*) Weil, P. E., and Bernard, J.: Le cancer de l'estomac chez les bierméries guéris, Presse méd. **43**:97, 1935. (*d*) Heath, C. W.: Treatment of Anemia in Inoperable Carcinoma of Stomach, M. Clin. North America **18**:1183, 1935. (*e*) Priestley, J. T., and Heck, F. J.: Bleeding Malignant Polypoid Lesions in the Cardia of the Stomach Associated with Severe Anemia: Report of Three Cases, Ann. Surg. **101**:839, 1935.

85. Goldhamer, S. M.: Unpublished data.

INFECTION

A disturbance in the balance between the production and the destruction of the red blood cells may be caused by infection. Usually secondary anemia results. The response of the leukopoietic tissue to infection depends on the state of the bone marrow and on the type of infection.[86] The total white blood cell count may be used as an index of the degree of response of the bone marrow, the maturity or immaturity of the leukocytes as a measure of the effort of response of the leukopoietic tissue and the number of polymorphonuclear neutrophils with cytoplasmic changes as an index of the severity of the infection. In following the course of an infection it appears that more information can be obtained by determining such changes in the cytoplasm of the white blood cells as vacuolation, toxic granulation and the presence of a bluish or grayish color of the cytoplasm than by noting the number of lobes or filaments of the nuclei.[87]

ENDOCRINE DISTURBANCES

Clinically it has been observed by some authors that specific changes in the blood are associated with hyperthyroidism; however, there appears to be a wide divergence of opinion concerning this fact. The anemia often noted in association with myxedema may be macrocytic or microcytic and may be directly related to the dysfunction of the thyroid gland or may exist as an independent condition. The possibility that macrocytic anemia is caused by a decrease in gastric function was investigated, and it was noted that in patients with endocrine dysfunction gastric secretion may be normal or reduced.[15] Anemia has also been reported in association with the syndrome of menstrual disorder and low metabolic rate without myxedema.[88] Marked improvement in this type of anemia was obtained with thyroid medication and also with large doses of iron.[89]

Experimentally[90] it was demonstrated that intravenous or intramuscular injections of an extract prepared from the posterior lobe of

86. Bethell, F. H.: The Response to Infection in Bone Marrow Dyscrasias, J. Lab. & Clin. Med. **20**:362, 1935.

87. Meranze, D. R.; Mendell, T. H., and Meranze, T.: Cytoplasmic Changes in the Peripheral Neutrophil as an Aid in Diagnosis and Prognosis, Am. J. M. Sc. **189**:639, 1935. Haden, R. L.: Qualitative Changes in Neutrophilic Leukocytes, Am. J. Clin. Path. **5**:354, 1935. Bethell.[86]

88. Haines, S. F., and Mussey, R. D.: Certain Menstrual Disturbances Associated with Low Basal Metabolic Rates Without Myxedema, J. A. M. A. **105**: 557 (Aug. 24) 1935.

89. Unpublished data, Simpson Memorial Institute.

90. Dodds, E. C., and Noble, R. L.: Relation of the Posterior Lobe of the Pituitary Gland to Anaemia and to Blood Formation, Nature, London **135**:788, 1935. Dodds, E. C.; Hills, G. M.; Noble, R. L., and Williams, P. C.: The Posterior Lobe of the Pituitary Gland: Its Relationship to the Stomach and to the Blood Picture, Lancet **1**:1099, 1935.

the pituitary gland caused hemorrhage in the acid-bearing area of the stomach, severe macrocytic anemia, reticulocytosis, hyperplasia of the bone marrow, leukocytosis and an increase in the production of bile. The authors hypothesized that the pituitary gland may control hematopoiesis by its effect on the stomach and reticulo-endothelial system, and this may account for the changes in the blood seen in association with disorders of the pituitary gland.

After adrenalectomy in rats [91] the peripheral blood showed an increase in the number of platelets and leukocytes, a slight increase in the number of lymphocytes and a slight reduction in the number of polymorphonuclear leukocytes. The injection of an extract of the adrenal cortex into normal rabbits did not alter the number of leukocytes.[92] In view of the stimulating effect of epinephrine on the leukopoietic system, a simple test was devised for clinical purposes to distinguish catarrhal from other forms of jaundice.[93] Usually leukopenia is present in cases of catarrhal jaundice. Whereas the injection of 1 cc. of a 1:1,000 solution of epinephrine produced an increase of from 50 to 300 per cent in the number of white blood cells, in cases of catarrhal jaundice there is often no increase and never more than a 40 per cent rise in the total number of leukocytes.

IRON DEFICIENCY ANEMIA

The value of iron as a specific remedy for a frequent type of anemia has continued to receive recognition. Davidson, Fullerton and Campbell,[94] after adopting standards for normal values for hemoglobin and erythrocytes at the various age groups in both sexes, examined 3,500 persons, representing a cross-section of the poor of Aberdeen. They found anemia to be relatively infrequent, except in infants between the eleventh and the twenty-third month of life and in adult women. Abnormally low values were found in 41 per cent of infants under 2 years of age, 32 per cent of children of preschool age, 16 per cent of adolescent women and 45 per cent of adult women. The incidence

91. Shecket, H. A.; Friedman, D. L., and Nice, L. B.: Number of Thrombocytes and Leucocytes in Blood and Adrenalectomized Rats, Proc. Soc. Exper. Biol. & Med. **32**:608, 1935.

92. Fox, C. A., and Whitehead, R. W.: Effect of Cortico-Adrenal Extract on Leukocytes in Blood of Normal Adult Rabbits, Proc. Soc. Exper. Biol. & Med. **32**:756, 1935.

93. Weiner, J. G.: The Adrenalin-Leucocyte Count in Catarrhal Jaundice, M. Rec. **141**:453, 1935.

94. Davidson, L. S. P.; Fullerton, H. W., and Campbell, R. M.: Nutritional Iron Deficiency Anemia with Special Reference to Prevalence and Age and Sex Incidence, Brit. M. J. **2**:195, 1935.

of anemia was greatest among women of the reproductive age who had borne children; it became progressively less after the menopause. Anemia was not found in adolescent and adult males, except in association with organic disease.

The prevalence of anemia in early childhood has been generally attributed to the low iron content of the usual infant diet coupled with the demand occasioned by rapid growth. These, undoubtedly, are important factors, but, as in the case of adults, diminished gastric secretion of hydrochloric acid may play an important rôle in causing nutritional anemia. Following an earlier report of Hawksley, Lightwood and Bailey, Ogilvie [14] found that of 13 young children with achlorhydria or hypochlorhydria 11 suffered from anemia of the iron deficiency type. On the other hand, of 18 patients with anemia of this type 10 secreted acid in normal quantities. They concluded that a diet poor in iron may be a sufficient single cause for nutritional anemia in children but that, furthermore, in spite of an ordinarily adequate supply of iron-containing food, anemia may develop as the result of gastric secretory defect. A similar study made by Faber, Mermod, Gleason and Watkins [95] led them to the supposition that the physiologic hypochlorhydria present in the first two years of life may cause poor absorption of iron-containing food, resulting in inadequate production of hemoglobin. In a discussion of anemia in children, Parsons and Smallwood [96] attributed nutritional anemia in the great majority of cases to a lack of iron. They recommended the use of 0.2 Gm. of reduced iron daily or 1 Gm. of ferrous sulfate daily. In some cases it is advisable, according to these authors, to supplement iron medication with yeast. The value of copper in the treatment of nutritional anemia in children has not been conclusively established, although recently its use has been advocated by Elvehjem, Siemers and Mendenhall.[97] They studied children with a hemoglobin content ranging from 9 to 11 Gm. per hundred cubic centimeters of blood. These values were raised to from 12 to 13.5 Gm. They found a combination of ferric pyrophosphate and cupric sulfate, yielding 25 mg. of metallic iron and 1 mg. of metallic copper daily to be particularly efficacious. The response to iron alone was found to be slower than when copper was used. They stated that the use of large doses

95. Faber, H. K.; Mermod, C.; Gleason, A. L., and Watkins, R. P.: Microcytic, Hypochromic (Iron-Deficiency) Anemia in Infancy and Childhood: Its Relation to Gastric Anacidity and to Simple Achlorhydric Anemia of Adults, J. Pediat. **7**:435, 1935.

96. Parsons, L. G., and Smallwood, W. C.: The Anaemias of Infancy and Childhood, Practitioner **134**:298, 1935.

97. Elvehjem, C. A.; Siemers, A., and Mendenhall, D. R.: Effect of Iron and Copper Therapy on Hemoglobin Content of the Blood of Infants, Am. J. Dis. Child. **50**:28 (July) 1935.

of iron is undesirable because of its interference with the assimilation of phosphorus. On the other hand, the studies of Sachs, Levine and Fabian [98] indicate that an inverse relationship of the iron and copper content of the blood may exist in persons with hypochromic anemia. They found no evidence of a depletion of copper.

Idiopathic hypochromic anemia, as a distinct clinical entity, has, during the past year, received less attention than formerly. It is now generally grouped with the hypochromic and microcytic anemias prevalent in middle-aged women, which are due to a variety of factors, including dietary defect, lack of hydrochloric acid in the stomach, menorrhagia and repeated pregnancy. In a discussion of this condition Schulten [99] emphasized the value of large doses of iron and pointed out the relatively greater efficacy of the ferrous salts over the elemental and ferric forms of the metal. He advocated the use of 10 Gm. of reduced iron daily or from 0.5 to 1 Gm. of ferrous chloride daily. Such an amount of reduced iron is undoubtedly excessive, since it has been shown that 1.5 Gm. of reduced iron, even in the presence of achlorhydria, will cause an average gain in hemoglobin of 153 mg. per hundred cubic centimeters, or approximately 1 per cent, daily.[64] Moreover, the ingestion of large amounts of metallic iron is undesirable from a mechanical point of view alone, since Sjöberg [100] has demonstrated that it may result in intestinal obstruction.

Dysphagia complicating hypochromic anemia, known as the Plummer-Vinson syndrome, is often attributable to a mechanical obstruction of the upper portion of the esophagus, according to Hoover.[101] He advised dilatation of the esophagus together with iron medication for the relief of this condition. However, it has been the experience of most observers that the dysphagia will be relieved on improvement of the anemia.

The rôle of the stomach in the assimilation of iron has received additional emphasis from the investigations of Fasiani and Chiatellino.[102] They reported the results of studies of the blood of a large group of patients treated by operation for gastroduodenal ulcer. In many persons, especially in women, partial gastric resection led after a number of years to hypochromic anemia with all the characteristics of idiopathic hypo-

98. Sachs, A.; Levine, V. E., and Fabian, A. A.: Copper and Iron in Human Blood, Arch. Int. Med. **55**:227 (Feb.) 1935.

99. Schulten, H.: Zur Klinik der essentiellen hypochromen Anämie, München. med. Wchnschr. **82**:697, 1935.

100. Sjöberg, H.: Symptoms of Ileus from Retention of Iron in Cecum Following Administration of Large Doses of Iron, Acta med. Scandinav. **85**: 129, 1935.

101. Hoover, W. B.: The Syndrome of Anemia, Glossitis, and Dysphagia: Report of Cases, New England J. Med. **213**:394, 1935.

102. Fasiani, G. M., and Chiatellino, A.: Syndromes anémiques chez les opérés de l'estomac, Presse méd. **42**:2080, 1934.

chromic anemia, including achlorhydria, and often to changes in the tongue and nails. The anemia occurred most frequently after a Billroth (no. 2) or a Polya operation, which involves more extensive removal of the stomach.

Although the classification of anemia on the basis of the size and hemoglobin content of the red blood cells offers definite advantages and has recently been reemphasized by Haden,[103] it is unjustifiable to use such a classification as an exclusive therapeutic guide. Hypochromia and microcytosis reflect the status of the blood-forming organs rather than denote the lack of a single substance required for hematopoiesis. The possible influence of dietary deficiencies other than deficiency of iron in causing anemia or in retarding regeneration of the blood has been emphasized by Sturgis and Farrar,[104] by Baker[105] and particularly by Minot.[106] Minot has also suggested that iron may be of benefit other than as simply supplying a deficiency. In this connection it is of interest that a group of French investigators[107] have reported benefit from the use of iron in the treatment of patients suffering with lassitude, digestive disorders and glossitis, even though such patients had no anemia. They have observed, after iron medication, restoration of the papillae of the tongue and, in 1 case in which gastroscopy was done before and after treatment, correction of atrophy of the gastric mucosa.

DEFINITE DISEASE ENTITIES OF THE BLOOD

POLYCYTHEMIA

Headache, dizziness and paresthesia may be the presenting symptoms of polycythemia (Adams[108]). Splenomegaly is always associated with this condition, and hepatomegaly is frequently present. There is a tendency to bleed easily. In Adams' series, every patient subjected to a surgical procedure suffered from postoperative hemorrhage. For

103. Haden, R. L.: Hypochromic Anemia, Ohio State M. J. **31**:583, 1935.

104. Sturgis, C. C., and Farrar, G. E.: Hemoglobin Regeneration in the Chronic Hemorrhagic Anemia of Dogs (Whipple): The Effect of Iron and Protein Feeding, J. Exper. Med. **62**:457, 1935.

105. Baker, J. P., Jr.: Anemias Dependent upon Food Deficiencies, Virginia M. Monthly **62**:335, 1935.

106. Minot, G. R.: The Anemias of Nutritional Deficiency: Etiology, Diagnosis, Treatment and Prevention, J. A. M. A. **105**:1176 (Oct. 12) 1935.

107. (*a*) Chevallier, P.; Moutier, F.; Stewart, W.; Sevaux, A., and Ely, Z.: L'atropie gastrique et la thérapeutique antianémique dans des affections sans anémie: Conception d'une maladie à manifestations diverses dont les anémies essentielles ne sont que des formes cliniques graves, Bull. et mém. Soc. méd. d. hôp. de Paris **50**: 1606, 1934. (*b*) Chevallier, P.; Moutier, F., and Ely, Z.: Un cas de chlorose fruste de la puberté avec atrophie gastrique cliniquement latente, Sang **9**:748, 1935.

108. Adams, L. J.: Polycythemia Vera, with Special Reference to Nervous Manifestations: Analysis of Nine Cases, Canad. M. A. J. **32**:128, 1935.

treatment, Adams used phenylhydrazine hydrochloride and roentgen irradiation over the long bones in small repeated doses. Langer,[109] postulating that polycythemia is due to an imbalance of the vegetative nervous system, irradiated the paravertebral ganglions (vertebral column). There was a decrease in the red cell blood count during the months following cessation of the roentgen treatment. Nisbet [110] also advocated roentgen therapy for this condition.

Weber [111] described a patient who had erythremia, migraine, gout and thrombophilia. At one time the symptoms, together with tarry stools, suggested duodenal ulcer, but no bleeding points were discovered at autopsy. There was a tendency to thrombus formation, and this accounted for many of the symptoms. Wilbur and Ochsner [112] found 12 instances of peptic ulcer (10 of duodenal and 2 of gastric) in 143 patients with polycythemia, as compared with from 2 to 3.2 per cent in a control group.

Lunedei and Liesch [113] attributed polycythemia and gastroduodenal ulcer to diencephalic hypofunction. They noted gastroduodenal ulcer, essential polycythemia and Fröhlich's syndrome in various members of the same family. Singer [114] noted the disappearance of polycythemia after gastric resection in a patient in whom the disease was associated with peptic ulcer.

As to the etiology, Beyne, Binet and Strumza [115] stated that anoxemia is the primary feature and that polycythemia is of respiratory origin. Reznikoff, Foot and Bethea [116] noted distinct capillary thicken-

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109. Langer, H.: Roentgen Therapy in Hyperplastic Blood Dyscrasias: New Technique for Myeloid and Lymphatic Leukemia, Polycythemia Rubra Vera and Hodgkin's Disease, Am. J. Roentgenol. **34**:214, 1935.

110. Nisbet, A. T.: Treatment of Blood Dyscrasias by X-Radiation, J. Cancer Research Com., Univ. Sydney **6**:201, 1935.

111. Weber, F. P.: Erythrämie mit Migräne, Gicht und Thrombophilie, Klin. Wchnschr. **14**:15, 1935.

112. Wilbur, D. L., and Ochsner, H. C.: Association of Polycythemia Vera and Peptic Ulcer, Ann. Int. Med. **8**:1667, 1935.

113. Lunedei, A., and Liesch, E.: Ulcera gastro-duodenale policitemia essenziale, sindrome adiposo-genitale di Froehlich in vari membri di una stessa famiglia: Considerazione sull' importanza delle disfunzioni diencefaliche nella patogenesi dell' ulcera gastro-duodenale e della poliglobulia e sui rapporti fra queste, Riv. di clin. med. **36**:485, 1935.

114. Singer, Karl: Gibt es eine gastrogene Polyglobulie? Klin. Wchnschr. **14**:751, 1935.

115. Beyne, J.; Binet, L., and Strumza, M. V.: Sur le mécanisme de la polyglobulie d'origine respiratoire, Compt. rend. Soc. de biol. **118**:1177, 1935.

116. Reznikoff, P.; Foot, N. C., and Bethea, J. M.: Etiologic and Pathologic Factors in Polycythemia Vera, Am. J. M. Sc. **189**:753, 1935.

ing, probably fibrosis, in the bone marrow of 7 patients with polycythemia and 6 showed, in addition, marked subintimal and adventitial fibrosis of the subarteriolar capillaries, arterioles and arteries. Slight thickening of the capillaries was seen in the agranulocytic bone marrows of 3 of 5 patients. In cases of general arteriosclerosis medial fibrosis was also evident. The authors concluded that "the vascular changes, especially in the capillaries of the bone marrow in polycythemia vera patients, suggest the possibility that these lesions may result in anoxemia of the bone marrow with compensatory or excess compensatory polycythemia."

Sgalitzer[117] treated patients with polycythemia with "total irradiation." He gave treatments of twenty minutes each to the whole body (except the eyes and genitalia), applying about 25 roentgens to the surface of the body. These were given for six successive days, with weekly intervals between courses. Treatment was discontinued before the leukocyte count fell to below 3,000 per cubic millimeter. There was symptomatic improvement, with relapse in from eighteen months to five years. In the patient treated by Bishop, Bishop and Trubeck,[118] roentgen irradiation of the long bones and spleen appeared to be associated with a gradual increase in the red blood cell count rather than a reduction, although there was subjective improvement.

Reimann and Breuer[119] advocated venesection, with removal of from 300 to 400 cc. of blood, twice weekly until the hemoglobin content has fallen to from 80 to 90 per cent. They reported excellent remissions with the effects persisting for approximately two years. The treatment aims to deplete the body of stores of blood-forming materials.

In a case of nonfamilial erythremia, Briggs and Oerting[10] produced a remission with gastric lavage from four to six times daily. In cases of familial erythremia this procedure relieved the symptoms and prevented an increase in the red blood cell count.

Tyler and Baldwin[120] produced polycythemia in rats by exposing them to atmospheres low in oxygen for from two to fifteen days. After normal pressure was again used, 50 per cent of the excess erythrocytes disappeared within six hours. Possible explanations were (1) the absorption of the blood by some organ, (2) dilution of plasma and (3) restoration to normal after a period of anhydremia.

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117. Sgalitzer, M.: Röntgentotalbestrahlung bei Polycythämie, Wien. klin. Wchnschr. **48**:675, 1935.

118. Bishop, L. F.; Bishop, L. F., Jr., and Trubeck, M.: Erythremia, Ann. Int. Med. **8**:1602, 1935.

119. Reimann, F., and Breuer, A.: Die Aderlassbehandlung der Erythrämie, Eine therapeutische Untersuchung, Ztschr. f. klin. Med. **128**:238, 1935.

120. Tyler, D. B., and Baldwin, F. M.: Rate of Disappearance of Red Cells in Polycythemic Rats, Proc. Soc. Exper. Biol. & Med. **33**:165, 1935.

ABNORMALITIES OF BLOOD CLOTTING

Several interesting experiments relating to coagulation of the blood have been performed in vitro.[121] As a result of these observations Eagle concluded that thrombin is the cause of coagulation and is an enzyme; that prothrombin is the precursor of thrombin; that the blood platelets accelerate the rate of the formation of thrombin, although their mode of action is not known, and that there is no evidence of species-specific activity of platelets in the transformation of thrombin. It was also demonstrated that all the elements of hemophilic blood which partake in coagulation are normal and that the deficiency of the clotting mechanism in hemophilic blood is probably the result of the slow formation of thrombin.[122] A most comprehensive review by Howell concerning the theories of blood coagulation has recently been published.[123]

Since the chemical nature of the various elements which are involved in blood clotting are known, it has been recommended that diets high in protein and fat be given to persons in whom there is a deficiency of the blood-clotting mechanism.[124]

PURPURA HAEMORRHAGICA

Many etiologic factors may cause purpura, and various forms have been classified. The clinical value of these complex classifications is somewhat doubtful. The degree of bleeding is determined by three factors: (*a*) the platelets, (*b*) the permeability of the capillaries and (*c*) the plasma. The diminution in the number of platelets may be due to a deficient formation in the bone marrow[125] or to increased destruction by the reticulo-endothelial system (primarily the spleen). The disturbance of formation of the platelets in the bone marrow has been ascribed to a hormonal deficiency, resulting in the failure of the megakaryoblasts to maturate. The decrease in the number of platelets is thought by some to be the result of hemorrhage rather than the

121. Eagle, H.: Studies on Blood Coagulation: The Rôle of Prothrombin and of Platelets in the Formation of Thrombin, J. Gen. Physiol. **18**:531, 1935; Studies on Blood Coagulation: The Formation of Fibrin from Thrombin and Fibrinogen, ibid. **18**:547, 1935.

122. Eagle, H.: Studies on Blood Coagulation: The Nature of the Clotting Deficiency in Hemophilia, J. Gen. Physiol. **18**:813, 1935.

123. Howell, W. H.: Theories of Blood Coagulation, Physiol. Rev. **15**:435, 1935.

124. Kugelmass, I. N.: "Bleeding" and "Clotting" Diets, M. Clin. North America **19**:989, 1935.

125. Willie, H.: Ueber den Bau und die Funktion der Megakaryocyten und ihre Beziehungen zur thrombopenischen Purpura, Folia haemat. **53**:426, 1935.

cause, the thrombocytes being withdrawn from the circulation and fixed in the bleeding areas as a defense mechanism.[126]

Both hereditary[127] and acquired[128] types of thrombocytopenic purpura have been described. In many instances the etiology is not known. Usually it is associated with disease of the bone marrow[125] or spleen or is the result of infection or drugs.[128d] Purpura associated with alterations in the permeability of the vascular membranes may be the result of allergy,[129] food deficiency, infection[128a] or toxins. The determination of the causal factor of purpura before institution of treatment is most important, and since this cannot always be accomplished failure of therapy may result.

Splenectomy, although usually associated with remarkable improvement in cases of thrombocytopenic purpura, may also be of no benefit.[130] If the spleen is overactive and destroys the platelets in excess numbers, its removal is indicated; however, if the decrease in the number of thrombocytes is the result of a disturbance in the production of platelets in the bone marrow, splenectomy is of little value. Because of the high mortality rate associated with splenectomy, ligation of the splenic artery has been recommended as a substitute.

Bleeding associated with food deficiency may be alleviated by a well balanced diet, especially one rich in vitamins and having a high protein and high fat content.[124] Foci of infection and sources of toxins should be removed. Successful results have been reported by desensitization and removal of the cause in persons with purpura due to allergy.[128] Viosterol and halibut liver oil are of no value.[131] Snake venom[132] has

126. Rolleston, H.: The History of Haematology, Proc. Roy. Soc. Med **27**:1161, 1934.

127. (*a*) Bailey, F. R., and McAlpin, K. R.: Familial Purpura: Report of Two Cases, Am. J. M. Sc. **190**:263, 1935. (*b*) Farber, Jason E.: Familial Hemorrhagic Condition Simulating Hemophilia and Purpura Hemorrhagica, Am. J. M. Sc. **188**:815, 1934.

128. (*a*) Traut, E. F.: Hypersensitivity in Rheumatic Disease: Henoch's Purpura with Erythema Nodosum; Rheumatic Fever; Migraine, State of Hypersensitivity to Ingesta, M. Clin. North America **18**:1237, 1935. (*b*) Eyermann, C. H.: Allergic Purpura, South. M. J. **28**:341, 1935. (*c*) Brown, O. H.: Purpura Hemorrhagica from Food Sensitization: Successful Treatment by Dietary Regulation and Use of Digestants; Case Report, Southwestern Med. **19**:131, 1935. (*d*) Hudson, E. H.: Purpura Haemorrhagica Caused by Gold and Arsenical Compounds, with Report of Two Cases, Lancet **2**:74, 1935.

129. Eyermann.[128b] Brown.[128c]

130. Unpublished data, Simpson Memorial Institute.

131. Jones, H. W., and Rathmell, T. K.: Purpura Hemorrhagica: Effect of Viosterol on Blood Platelets, Tr. A. Am. Physicians **49**:277, 1934.

132. Peck, S. M., and Rosenthal, N.: Effect of Moccasin Snake Venom (Ancistrodon Piscivorus) in Hemorrhagic Conditions, J. A. M. A. **104**:1066 (March 30) 1935. Greenwald, H. M.: Dilute Snake Venom for the Control of Bleeding in Thrombocytopenic Purpura, Am. J. Dis. Child. **49**:347 (Feb.) 1935.

been employed in many instances. The results are conflicting, and there are insufficient data at present to estimate their clinical worth. Since spontaneous cure is not uncommon, a conservative attitude must be adopted concerning the value of the various therapeutic agents recommended.

HEMOPHILIA

Hemophilia is diagnosed by the following features: heredity, occurrence in males, a history of repeated hemorrhages,[133] prolonged clotting time and normal bleeding time. There is considerable diversity of opinion regarding the nature of the blood elements concerned with the clotting mechanism in hemophilia.[134] It was recently demonstrated that all the elements are normal but that the formation of thrombin is delayed.[122] Some authors have expressed the belief that the disease is due to faulty development of the liver, while others have stated that it is caused by an endocrine deficiency.

Included in the group of diseases associated with abnormal bleeding, there is described a syndrome known as hereditary pseudohemophilia.[135] It is characterized by the following features: heredity, transmission by either sex, normal platelet count, positive reactions to the Rumpel-Leed and needle-prick tests, prolonged bleeding time and normal clotting time.

The histopathologic structure of the hematopoietic tissues in cases of hemophilia is quite interesting.[136] Studies of the bone marrow reveal an increase in the number of megakaryocytes, which do not appear to vary from the normal in morphology. The red blood cell-forming and white blood cell-forming tissues likewise appear normal. No abnormalities are detected in the blood vessels. With the exception of the prominence of the reticulo-endothelial system, no changes are evident in the spleen or lymph glands.

At present no known specific therapy exists. Some of the common agents employed are whole blood, citrated blood, human plasma, human and animal serum, defibrinated blood, hemostatic preparations, fibrinogen and cephalin in suspension, calcium chloride, sodium citrate, protein shock, liver and its derivatives, whole ovary and ovarian extracts and

133. Seligman, B.: Hematuria in Hemophilia, with Two Cases of Acute Nephritis, M. Rec. **141**:150, 1935.

134. Quick, A. J.: The Prothrombin in Hemophilia and in Obstructive Jaundice, J. Biol. Chem. **109**:73, 1935. Quick, A. J.; Stanley-Brown, M., and Bancroft, F. W.: A Study of the Coagulation Defect in Hemophilia and in Jaundice, Am. J. M. Sc. **190**:501, 1935.

135. Handley, R. S., and Nussbrecher, A. M.: Hereditary Pseudo-Haemophilia, Quart. J. Med. **4**:165, 1935.

136. Custer, R. P., and Krumbhaar, E. B.: The Histopathology of the Hemopoietic Tissues in Hemophilia: Unexplored Field, Am. J. M. Sc. **189**:620, 1935.

a special dietary regimen.[124] This therapy may be employed as a prophylactic and as treatment for the immediate hemorrhage.

Although it has been stated that the urine of persons with hemophilia does not contain the estrogenic hormone, all investigators do not agree with this fact.[137] The results obtained in the prevention of the episodes of bleeding with ovary, ovarian extracts and other tissue extracts have not been encouraging.[138] Sensitization with animal serum still remains the most satisfactory form of prophylactic therapy. Acute hemorrhages are best treated by compression, multiple transfusions, administration of epinephrine, repeated injections of whole blood into the buttocks and local application of snake venom.[139]

"BANTI'S DISEASE"

Banti in 1881 originally described the disease that is given his name as a distinct entity and stated that the course was divided into three stages, which lasted for several years. In 1894 he reported a more complete series of cases and modified his views somewhat. He postulated that the etiologic agent was an unidentified toxic substance carried to the spleen with secondary involvement of the liver. The pathologic changes noted were sclerosis of the splenic vessels, atrophy of the malpighian corpuscles, induration of the pulp, sclerosis of the portal system and atrophic cirrhosis of the liver. The treatment was splenectomy.

At the present time the existence of this disease is questioned. The pathologic changes which were thought to be specific by Banti have been produced experimentally [140] in animals by obstruction of the portal and splenic veins and have been demonstrated at autopsy to be secondary to hepatic disorders (cirrhosis) and thrombosis of the portal and splenic veins.[141] It has been suggested that the syndrome be termed hepatolienal cirrhosis.

The most commonly observed symptoms and signs are splenomegaly, weakness, hemorrhage, enlargement of the liver, jaundice and ascites. Cases have been reported in which the patient had intermittent painful

137. Chew, W. B.; Stetson, R. P.; Smith, G. V., and Smith, O. W.: Estrogenic, Luteal and Gonadotropic Hormones in Hemophilia, Arch. Int. Med. **55**:431 (March) 1935.

138. Novak, E.: The Therapeutic Use of Estrogenic Substances, J. A. M. A. **104**:1815 (May 18) 1935. Chew, Stetson, Smith and Smith.[137]

139. Peck, S. M.; Crimmins, M. L., and Erf, L. A.: Coagulating Power of Bothrops Atrox Venom on Hemophiliac Blood, Proc. Soc. Exper. Biol. & Med. **32**:1525, 1935.

140. McMichael, J.: Splenic Anemia, Edinburgh M. J. **422**:97, 1935.

141. Leinoff, H. D.: Splenic Vein Thrombosis and Its Relationship to Banti's Syndrome, with Report of a Case, Ann. Int. Med. **9**:85, 1935. McMichael.[140]

joints in addition to the anemia and splenomegaly.[142] The question has arisen whether arthritis is a coincidental finding; Fitz commented on the possible relationship of Banti's disease, Felty's syndrome, gout and Still's disease. In another case report he discussed the relationship of peptic ulcer and Banti's disease.[143]

The anemia present may be microcytic or macrocytic. Unquestionably the former type is due to chronic hemorrhage. Macrocytic anemia is probably the result of interference with hematopoiesis due to the failure of the liver to store or present for utilization to the bone marrow the substance necessary for the maturation of the red blood cells. It is felt by some that the anemia is the result of an increase in hemolysis. One author stated that in his particular case macrocytic anemia was due to a combination of changes in the thyroid and spleen.[144] The nature of the anemia following splenectomy has been studied experimentally in rats.[145] The investigator is of the opinion that the reticulo-endothelial system governs hematopoiesis and that hypochromic anemia resulting from the operation is due to a deficiency of hemoglobin. Hyperplasia of the reticulo-endothelial system aids in the storage of iron; thus the administration of iron will lessen the severity of the anemia but will not eliminate it.

For several years the accepted treatment for Banti's disease has been splenectomy. A résumé of the early reports is confusing as in many of the cases reported the condition does not fit into this syndrome. Furthermore, the disease itself may run a course lasting several years, so that any conclusions drawn concerning the benefits derived from this procedure must be guarded. Recently many authors have again emphasized the value of splenectomy in cases of Banti's disease.[146] The results obtained by workers at the University of Michigan Hospital[147] as well as those obtained by others,[148] do not seem to justify the con-

142. Fitz, R.: Three Cases with Intermittently Painful Joints, Splenomegaly and Anemia, M. Clin. North America **18**:1053, 1935.

143. Jennings, J. E.: Duodenal Ulcer and Banti's Disease; Diaphragmatic Hernia; Hirsute Virilism, Ann. Surg. **102**:138, 1935.

144. Serio, F.: Anémie tireosplenopatiche, Haematologica **16**:609, 1935.

145. Gottlieb, R.: Nature of Postsplenectomy Anaemia, Canad. M. A. J. **32**: 642, 1935.

146. Larrabee, R. C.: Chronic Congestive Splenomegaly and Its Relationship to Banti's Disease, Am. J. M. Sc. **188**:745, 1934. Ellis, R. W. B.: Anaemia Associated with Splenomegaly in Childhood, Practitioner **134**:317, 1935. Mills, E. S.: Blood Dyscrasias Amenable to Treatment by Splenectomy, Canad. M. A. J. **33**:480, 1935. Leinoff.[141] Jennings.[143]

147. Goldhamer, S. M.: Splenectomy in Hematopoietic Disorders, Univ. Hosp. Bull. Ann Arbor **2**:20, 1936.

148. (*a*) Watson, R. B.: Ligation of Splenic Artery for Advanced Splenic Anaemia, Brit. M. J. **1**:821, 1935. (*b*) McMichael.[140]

tinuation of this type of treatment. Ligation of the splenic artery has been recommended when the condition is far advanced.[148a] The administration of iron before and after splenectomy is offered as a method to reduce the mortality rate.[149] Because of the high mortality rate associated with splenectomy and the equally good results following conservative measures, it appears that the latter type of therapy would be preferable.

GAUCHER'S DISEASE

Three members of a family, a sister and two brothers, were studied by Kveim.[150] The ages were 23, 26 and 28 years. The symptomatology included hepatomegaly, splenomegaly, leukopenia, thrombopenia, an increase in the rate of sedimentation, a tendency to bleed, subperiosteal hemorrhages, petechiae on the lower extremities and brown discoloration of the exposed parts of the body. Gaucher cells were found in the bone marrow. In the sister there was a black discoloration of the instep and leg almost up to the knees, apparently associated with the hemorrhagic diathesis.

Special features of Gaucher's disease have been emphasized in several case reports. Involvement of the kidneys and splenomegaly were reported by Horsley, Baker and Apperly.[151] Sichel and Warter [152] and Merklen and Warter [153] each reported a case in an adult. The pseudobulbar syndrome was reported in an infant by Meyer.[154] De Castro-Freire,[155] Acuña and de Filippi [156] reported the effect of splenomegaly in a case. Cavazzutti, Cricco and Calandra [157] also reported a case.

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149. Davidson, L. S. P.: Iron in Treatment of Splenic Anaemia, Lancet **2**:593, 1934.

150. Kveim, A.: Three Cases of Gaucher's Disease, Norsk mag. f. lægevidensk. **96**:696, 1935.

151. Horsley, J. S., Jr.; Baker, J. P., Jr., and Aperly, F. L.: Gaucher's Disease of Late Onset with Kidney Involvement and Huge Spleen, Am. J. M. Sc. **190**:511, 1935.

152. Sichel and Warter: Un cas de maladie de Gaucher chez l'adulte, Bull. et mém. Soc. de radiol. méd. de France **22**:509, 1934.

153. Merklen, P., and Warter, J.: Esquisse de la maladie de Gaucher de l'adulte, Médecine **16**:233, 1935.

154. Meyer, R.: Nouveau cas de syndrome pseudo-bulbaire du nourrisson (maladie de Gaucher du nourrisson), Rev. neurol. **2**:612, 1934.

155. de Castro-Freire, L.: De la splénectomie dans la maladie de Gaucher, Arch. de méd. d. enf. **38**:163, 1935.

156. Acuña, M., and de Filippi, F.: Enfermedad de Gaucher en un lactante: Esplenectomía, Semana méd. **1**:735, 1935.

157. Cavazzutti, G. B.; Cricco, J. J., and Calandra, R.: Enfermedad de Gaucher, Rev. sud-am. de endocrinol. **17**:865, 1934.

NIEMANN-PICK'S DISEASE AND SCHÜLLER-CHRISTIAN'S SYNDROME

Esser [158] isolated diplococci from the blood of his patient with Niemann-Pick's disease. Klenk [159] studied the nature of the phosphatids and other lipoids of the brain and liver of a patient with Niemann-Pick's disease.

Radding [160] reported a case of Schüller-Christian's syndrome in which roentgen therapy was used; the patient was living and under observation for eleven years. Teperson [161] treated his patient with roentgen rays. In the cases of Smith [162] and Horsfall and Smith [163] the lesions of the bones were marked, and in the latter case there were exophthalmos and diabetes insipidus. A number of cases were described by Livingston,[164] Fraser [165] and Dauksys [166] and by others during the year.

HODGKIN'S DISEASE: LYMPHOBLASTOMA

A study of the numerous reports in the literature of cases of Hodgkin's disease revealed the condition in the following sites: abdomen (Bargen and Ochsner [167]); nervous system (Cooper [168]); testes (Townsend [169]); urinary passages, spleen, nasopharynx and bones

158. Esser, M.: Eigenartige bakteriologische Befunde im Blute eines Falles von Niemann-Pickscher Erkrankung, Zentralbl. f. Bakt. (Abt. 1) **134**:461, 1935.

159. Klenk, E.: Ueber die Natur der Phosphatide und anderer Lipoide des Gehirns und der Leber bei der Niemann-Pickschen Krankheit: XII. Mitteilung über Phosphatide, Ztschr. f. physiol. Chem. **235**:24, 1935.

160. Radding, M. B.: Schüller-Christian Disease After X-Ray Therapy, Living and Under Observation Eleven Years, Radiology **24**:591, 1935.

161. Teperson, H. I.: Xanthomatosis: Case of Schüller-Christian's Disease Treated by Irradiation, Radiology **25**:440, 1935.

162. Smith, L. A.: Xanthomatosis Involving Bone (Lipoid Histiocytosis): Case Reports and Roentgen Findings, Radiology **24**:521, 1935.

163. Horsfall, F. L., Jr., and Smith, W. R.: Schüller-Christian Syndrome: Lipoid-Granulomatosis with Defects in Bones, Exophthalmos, and Diabetes Insipidus, Quart. J. Med. **4**:37, 1935.

164. Livingston, S. K.: Schüller-Christian Disease (Xanthomatosis): Case Report, J. Bone & Joint Surg. **17**:1035, 1935.

165. Fraser, J.: Skeletal Lipoid Granulomatosis (Hand-Schüller-Christian's Disease), Liverpool Med.-Chir. J. (pt. 2) **42**:133, 1934; Brit. J. Surg. **22**:800, 1935.

166. Dauksys, J.: Xanthomatosis: Schüller-Christian's Disease, J. Missouri M. A. **32**:466, 1935.

167. Bargen, J. A., and Ochsner, H. C.: Abdominal Hodgkin's Disease: Report of a Case, M. Clin. North America **19**:423, 1935.

168. Cooper, E. L.: Hodgkin's Disease: Some Clinical Aspects, with Special Reference to Effects upon Haemopoietic Tissues and Nervous System, M. J. Australia **1**:585, 1935.

169. Townsend, W. G.: Hodgkin's Disease of Testes, Urol. & Cutan. Rev. **39**:853, 1935.

(Livingston [170]), and sternum. Thoracic involvement, amyloid degeneration, anemia, ocular lesions, paraplegia, diabetes insipidus and infiltration of the ureters with bilateral obstructive pyelonephritis (Beck [171]) were also reported in certain cases. A case of the hepatic form was reported, and in 2 cases itching was a symptom (Craver; [172] Melton [173]).

Potter [174] has analyzed the lymphoblastomas in terms of the cells involved. She subdivided Hodgkin's disease on this basis into endotheliomatous, reticular, cellular and sclerotic types. Specific "Hodgkin's cells" must be present to confirm the diagnosis. Hodgkin's disease, sarcoma arising from the reticulo-endothelium and leukemia are considered as three distinct entities.

Pulmonary lymphogranulomatosis may be confused at times with tuberculosis, but there are certain roentgenographic appearances which may aid in the differential diagnosis. Goia, Daniello and Hanganutz [175] noted that while the parenchymatous pulmonary lesions are not specifically characteristic, the constancy of mediastinal lesions and peribronchovesicular lymphangitis are diagnostic. The opaque peribronchial adhesions are usually larger and more rounded than the tuberculous lesions, and the former lesions as well as the perifocal congestive reactions regress readily with roentgen irradiation.

In Wheatley's [176] case Hodgkin's disease was kept under control for ten years with roentgen irradiation. Paraplegia developed, but almost complete relief was obtained with irradiation therapy.

In Loveman's [177] case cutaneous manifestations antedated the appearance of fever and adenopathy. Roentgen therapy was effective. The author considered that generalized exfoliative dermatitis or universal scaly erythroderma should always be regarded as a possible cutaneous

170. Livingston, S. K.: Hodgkin's Disease of Skeleton Without Glandular Involvement: Case Report Proved by Autopsy, J. Bone & Joint Surg. **17**:189, 1935.

171. Beck, D.: Hodgkin's Disease with Bilateral Obstructive Pyelonephritis Due to Infiltration of Ureters, J. Mount Sinai Hosp. **2**:126, 1935.

172. Craver, L. F.: Treatment of Itching in Hodgkin's Disease, M. Clin. North America **19**:967, 1935.

173. Melton, R. R.: Report of a Case of Hodgkin's Disease Presenting Pel Ebstein Type of Remittent Fever with Chills and Generalized Pruritis, J. Kansas M. Soc. **36**:140, 1935.

174. Potter, E. L.: Hodgkin's Disease, with Special Reference to Its Differentiation from Other Diseases of Lymph Nodes, Arch. Path. **19**:139 (Feb.) 1935.

175. Goia, I.; Daniello, L., and Hanganutz, M.: Considérations sur les formes pseudotuberculeuses de la lymphogranulomatose maligne, Arch. méd.-chir. de l'app. respir. **10**:283, 1935.

176. Wheatley, L. F.: Lymphoblastoma with Paraplegia and Prolonged Irradiation, J. A. M. A. **104**:460 (Feb. 9) 1935.

177. Loveman, A. B.: Cutaneous Manifestations of Lymphoblastomas: Report of a Case of Hodgkin's Disease, J. A. M. A. **104**:1583 (May 4) 1935.

manifestation of one of the lymphadenoses. In Wile and Stiles'[178] case, observed at intervals for at least thirteen years, the primary picture was that of mycosis fungoides, but characteristics of typical Hodgkin's disease ultimately developed, resulting in the patient's death. Comando[179] reported a case of primary isolated Hodgkin's disease, limited to the distal portion of the pars media and the proximal part of the pyloric portion of the stomach. A prolonged remission, without recurrence, followed removal of the lymphoblastomatous tissue.

Schwarz[180] stated that pregnancy and living at high altitudes are detrimental to patients with Hodgkin's disease. As opposed to large single doses of roentgen rays to circumscribed fields or total irradiation with a large dose, he outlined the treatment as follows: 1. Each focus should receive treatment. 2. Fractional doses should be given at intervals of one or two days. 3. The size of the field should not exceed 800 sq. cm. 4. The surface doses should not exceed 250 roentgens. 5. The controlling factors are the tolerance of the skin, the status of the blood and the general reaction, such as fever or nausea. 6. The appearance of new lesions should be noted. In cases in which the condition is refractory Schwarz gives thorium X, which, in combination with roentgen rays, may cause improvement in the patient's condition.

LEUKEMIA

Symptomatology.—Schwab and Weiss[181] noted neurologic signs in 20.5 per cent of 334 cases of leukemia. There were neurologic signs in only about 25 per cent of the cases in which there was histologic evidence of leukemic infiltration of the central nervous system. There was unilateral or bilateral palsy of the sixth and seventh nerves, and less frequently of the fifth, eighth, ninth, tenth, eleventh and twelfth nerves. Among other signs were absence of deep reflexes, presence of signs referable to the pyramidal tract, paresthesias and evidence of meningeal irritation. The signs may show rapid fluctuations. Changes in the spinal fluid, present in 73.6 per cent of 34 cases, consisted of an increase in the cell count, an increase in the protein content and elevation of pressure.

The changes in the fundi may range from slight enlargement of the retinal veins to extreme retinitis. Leukemic infiltration of the orbital

178. Wile, U. J., and Stiles, F., Jr.: Clinical Mutations in Lymphoblastomas, J. A. M. A. **104**:532 (Feb. 16) 1935.

179. Comando, H. N.: Primary Isolated Lymphogranulomatosis of Stomach: Report of Case, Arch. Surg. **30**:228 (Feb.) 1935.

180. Schwarz, G.: Ueber Röntgenbehandlung Lymphogranulomkranker, Wien. Arch. f. inn. Med. **27**:353, 1935.

181. Schwab, R. S., and Weiss, S.: The Neurologic Aspect of Leukemia, Am. J. M. Sc. **189**:766, 1935.

connective tissue may produce uniocular or binocular exophthalmos (Kreibig [182]). Symmetrical aleukemic lymphadenosis of the orbit was noted in a case reported by Dzigielewski.[183] Gross papilledema may be present in chronic myelogenous leukemia (Frank [184]).

In 11 cases of leukemia, Goldstein and Wexler [185] found that the retinal lesions were minimal; marked sheathing of the veins with exudation of leukocytes into the retina and optic nerve, fragmentation and necrosis of the walls of the larger vessels and marked infiltration of the choroid were noted in exceptional patients. Exophthalmos and edema of the conjunctivae may occur coincidentally with a marked increase in the blood count.

Diamond [186] reported leukemic changes in the brain (14 cases), and Mills [187] correlated the observations in 60 cases of acute lymphatic leukemia in children.

In reviewing the osseous changes in cases of lymphocytic, myelocytic and monocytic neoplasm, Doub and Hartman [188] summarized the observations as follows: (1) punched-out areas of bone destruction (myelogenous leukemia, aleukemic myelosis, chloroma, Hodgkin's disease, and lymphosarcoma), (2) erosion in the ends of the diaphyses of the long bones (lymphatic leukemia, aleukemic myelosis, chloroma and Hodgkin's disease), (3) pinpoint areas of decalcification or destruction (aleukemic myelosis, chloroma, usually in the flat bones, e. g., skull) and (4) erosion of the cortex from within the medullary canal (myelogenous leukemia). Other changes are osteosclerosis (aleukemic myelosis, Hodgkin's disease and myelogenous leukemia, occasionally in lymphatic leukemia); generalized osteoporosis (lymphatic leukemia, aleukemic myelosis and chloroma). In the differential diagnosis sympathetic neuroblastoma shows practically the same roentgenographic changes,

182. Kreibig, William: Ueber Bindehautveränderungen bei leukämischen Erkrankungen, Ztschr. f. Augenh. **84**:120, 1934.

183. Dzigielewski, K.: Ueber symmetrische aleukämische Lymphadenose der Orbita, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **50**:276, 1934.

184. Frank, T. J. F.: Leuchaemic Retinitis: Analysis of Eye Changes in Thirty-Five Cases of Leuchaemia, Together with Report of Gross Papilloedema in Case of Chronic Myelogenous Leuchaemia, M. J. Australia **1**:364, 1935.

185. Goldstein, I., and Wexler, D.: Histologic Observations on the Fundus in Leukemia, Arch. Ophth. **13**:26 (Jan.) 1935.

186. Diamond, I. B.: Leukemic Changes in Brain: Report of Fourteen Cases, Arch. Neurol. & Psychiat. **32**:118 (July) 1934.

187. Mills, S. D.: Acute Lymphatic Leucemia in Childhood: Study of Sixty Cases with Especial Reference to Cytologic Characteristics of Blood, J. Pediat. **6**: 634, 1935.

188. Doub, H. P., and Hartman, F. W.: Lymphocytic, Myelocytic and Monocytic Neoplasms: Roentgen Diagnosis and Treatment, J. A. M. A. **105**:942 (Sept. 21) 1935.

but metastatic carcinoma, multiple myeloma, osteogenic sarcoma, xanthomatosis, Gaucher's disease, Albers-Schönberg's disease and infection of the bone must be considered.

Osseous changes were noted by Craver and Copeland [189] in about 7 per cent of 86 patients with lymphatic leukemia but in only 1 of a group of 84 patients with myelogenous leukemia.

Baty and Vogt [190] studied the bones of 43 children roentgenographically. In 70 per cent there was a narrow zone of diminished density proximal to the metaphyses of the long bones. Two patients showed generalized osteoporosis, and 2 showed slight periosteal elevation. Neuroblastoma, with generalized miliary metastasis, may show a roentgenographic picture similar to that of leukemia. The pathologic changes in the bones have been studied by Erb.[191]

Abt [192] noted that leukemia during childhood presents certain difficulties in diagnosis. The diagnosis may be confused with that of diphtheria, ulcerative stomatitis, scurvy and endocarditis, pertussis, pneumonia, sepsis, von Jaksch's anemia, Cooley's Mediterranean erythroblastic anemia, infectious mononucleosis, mediastinal tumor, Niemann-Pick's essential lipoid histiocytosis, rheumatism, diarrhea, parotitis, appendicitis and aplastic anemia; but a thorough examination of the blood will usually serve to prevent a mistaken diagnosis. The acute types are more common in childhood; chronic myelogenous leukemia is seen occasionally and chronic lymphatic leukemia rarely. The symptoms in children include fever, headache, loss of appetite, vomiting, asthenia, progressive weakness and anemia, apathy, pain in the abdomen, bones or joints, bleeding (mucous membranes and skin), cervical adenopathy, stomatitis, nervous symptoms, occasional dyspnea and cough (mediastinal involvement), swelling of the submaxillary and lacrimal glands and leukemic infiltrations in the skin.

Fuchs [193] noted that the lymphocytosis and occasionally a palpable spleen during childhood may make the diagnosis of leukemia difficult. Severe pain, fever and inflammatory swelling of the joints may be observed. While enlargement of the lymph nodes may be present in association with arthropathy (acute articular rheumatism or Still's dis-

189. Craver, L. F., and Copeland, M. M.: Changes of Bones in Leukemias, Arch. Surg. **30**:639 (April) 1935.

190. Baty, J. M., and Vogt, E. C.: Bone Changes of Leukemia in Children, Am. J. Roentgenol. **34**:310, 1935.

191. Erb, I. H.: Bone Changes in Leukaemia: Pathology, Arch. Dis. Childhood **9**:319, 1934.

192. Abt, Arthur F.: The Diagnosis of Leukemia in Childhood, Pennsylvania M. J. **38**:389, 1935.

193. Fuchs, B.: Ueber Gelenkerscheinungen bei kindlicher Leukämie, Monatschr. f. Kinderh. **63**:185, 1935.

ease), it should suggest study for leukemia. Areas of lesser density in the bones may be confirmatory of the diagnosis of leukemia. Osteitis fibrosa and Gaucher's disease may show similar roentgenographic changes.

Dumitrescu and Petrea [194] described a case of acute leukemia which simulated acute articular rheumatism.

Pain in the joints, without visible evidence of inflammation in children with leukemia, may sometimes make the differentiation from rheumatic disease difficult, unless the blood picture is characteristic. The pains may be migratory and vague, without evidence of changes roentgenographically. Smith [195] suggested that in the initial stages pain is due to increased pressure within the bone from the crowding of the hyperplastic marrow. The second step is rarefaction of the bone, followed by elevation of the periosteum from the spread of leukemic cells. Abnormal lymphocytes of a specific type may be present in the peripheral blood of patients of this type. Sutton and Bosworth [196] reported a case of lymphatic leukemia resembling rheumatic fever in a child.

In the diagnosis of leukemia, especially in the absence of characteristic changes in the blood, material obtained by sternal puncture (Löwinger [197]) or by splenic puncture (Perles; [198] Weil, Isch-Wall and Perles; [199] Papafotis [200]) may be of aid in determining the nature of the disease. Cells may be identified by the quantitative oxidase reaction (Nagel [201]), by the presence of Auer bodies (Lovisato; [202] Hawksley [203]), by the supravital staining characteristics (Lightwood, Hawksley

194. Dumitrescu, T., and Petrea, C.: Leucémie aiguë simulant le rheumatisme, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:957, 1934.

195. Smith, C. H.: Leucemia in Childhood with Onset Simulating Rheumatic Disease, J. Pediat. **7**:390, 1935.

196. Sutton, L. P., and Bosworth, O.: Lymphatic Leucemia Resembling Rheumatic Fever in Child: Report of Case, J. Pediat. **5**:61, 1934.

197. Löwinger, S.: Clinical Importance of Sternal Puncture: Bone Marrow Picture of Acute Myeloblastic Leukemia Associated with Leukopenia, Gyógyászat **75**:455, 1935.

198. Perles, S.: La ponction de la rate dans les maladies du sang, Paris méd. **2**:217, 1935.

199. Weil, P. E.; Isch-Wall, P., and Perles, S.: La ponction de la rate dans la myélomatose, Sang **9**:347, 1935; Un cas de leucémie aiguë sans modifications sanguines diagnostiqué par la ponction de la rate, ibid. **9**:213, 1935.

200. Papafotis, C.: La ponction de la rate et son importance pour l'étude étiologique des leucémies, Bull. méd., Paris **49**:399, 1935.

201. Nagel, W.: Untersuchungen über den quantitativen Oxydasegehalt der neutrophilen Blutleukocyten bei akuten Infectionen und leukämischen Myelosen, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **47**:228, 1935.

202. Lovisato, L.: Tre casi di leucemia acuta con corpi di Auer, Minerva med. **2**:84, 1935.

203. Hawksley, J. C.: Note on Occurrence of Auer's Bodies in Monocytic Leukaemia, J. Path. & Bact. **40**:365, 1935.

and Bailey [204]) or by peculiar inclusions in nonmature leukocytes (Yanonsky [205]).

Leukemia was first discovered in a patient of Rösler's [206] after trauma. Priapism was a marked feature. Improvement followed irradiation and the administration of arsenic. The author said that malaria, gas poisoning or trauma may cause leukemia; his patient was exposed to all three agents.

Carnot, Caroli and Busson [207] found splenic puncture a valuable aid in the diagnosis of aleukemic myelomatosis. In this condition there is a hepatosplenic association in the pathologic process which is characteristic of the disease.

Flinn [208] described a case of acute lymphatic leukemia of eight months' duration in a child of 4 years. There was a stage of extreme neutropenia, with slight but definite improvement after pentnucleotide therapy. An attack of rubella appeared to initiate a leukopenic phase, while a final leukemic stage accompanied an attack of acute follicular tonsillitis.

Bertelsen [209] described a case of acute leukemia in a 2 months old infant.

Jørgensen [210] reported a case of lymphatic leukemia in a shoemaker. The rôle of gaseous toxic substances, such as benzene, was considered. There was hyperplasia of all the preformed lymphatic tissue in all the organs.

De Marval [211] presented data that favor the infection theory of the origin of leukemia.

Weinstein and Fitz-Hugh [212] found that a low or normal titer of heterophile antibody is characteristic of leukemia, Hodgkin's disease, lymphosarcoma, polycythaemia vera, agranulocytic angina, typhoid,

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204. Lightwood, R.; Hawksley, J. C., and Bailey, U. M.: Supravital Staining in Diagnosis of Leukemias, Proc. Roy. Soc. Med. **28**:405, 1935.

205. Yanonsky, D.: Des inclusions particulières dans les leucocytes non mûrs dans les cas de leucémie aiguë, Sang **9**:610, 1935.

206. Rösler, O.: Traumatische Leukämie und Priapismus, München. med. Wchnschr. **82**:217, 1935.

207. Carnot, P.; Caroli, J., and Busson, A.: La myélose hepatosplénique aleucémique: Son diagnostic par la ponction de la rate, Paris méd. **1**:449, 1935.

208. Flinn, L. B.: Acute Lymphatic Leukemia in a Child of Four Years with Severe Granulopenic Stage Preceding Remission, Ann. Int. Med. **9**:458, 1935.

209. Bertelsen, A.: Case of Acute Leukemia in Infant Two Months Old, Ugesk. f. læger **97**:798, 1935.

210. Jørgensen, J. Vesterdal: Case of Acute Lymphatic Leukemia with Extensive Infiltrates in Gastro-Intestinal Canal, Ugesk. f. læger **97**:327, 1935.

211. De Marval, L.: Remisión, estado de equilibrio y recidiva en la leucemia mieloide crónica, Actas y trab. d. Cong. nac. de med. **3**:789, 1934.

212. Weinstein, G. L., and Fitz-Hugh, T., Jr.: The Heterophile Antibody Test in Leukemia and Leukemoid Conditions, Am. J. M. Sc. **190**:106, 1935.

simple adenitis, syphilis, tuberculosis and anemia. Slight increase in the heterophile antibody was noted in the serum of a patient with acute leukemia who had received twenty-eight transfusions of blood. High titers were noted in serum sickness and acute infectious mononucleosis. The parenteral administration of horse serum raised the titer in patients with chronic myelogenous leukemia and in nonleukemic persons, but not in patients with chronic lymphatic leukemia and lymphosarcoma or in a patient with atypical Hodgkin's disease.

Henschen and Jezler [213] found the enlargement of the liver and spleen to be of aid in the differential diagnosis between aleukemic leukemia and the aplastic forms of anemia, especially in those cases in which but few immature cells appear in the blood stream.

In cases of malignant tumors of lymphoid organs, Rubnitz [214] found that cells may enter the blood stream and give a leukemoid picture. In the early stages the other blood elements are normal, differentiating this condition from true leukemia, but in the advanced stages, with the involvement of the entire hematopoietic apparatus, the picture becomes more like that of a true leukemia. Lymphosarcoma is more likely to give a leukemoid reaction than epithelial tumors.

From specimens of lymph nodes taken for biopsy during the course of the disease in a patient with lymphatic leukemia, Stasney and Downey [215] concluded: The first step in the leukemic process is a diffuse proliferation of reticulum. The blood picture parallels the histologic changes in the glands, with predominance of specific cell types. The syncytial reticulum cells retain an embryonic hematopoietic potency.

The renewed interest in agranulocytosis has called forth many reports on the agranulocytic phases of leukemia and the differential diagnosis from the true malignant neutropenia (Jackson; [216] Julliard; [217] Kerlin; [218] Mitchell and Ramey; [219] Monfort; [220] Reaud and Prado; [221]

213. Henschen, C., and Jezler, A.: Aleukämische Myelose unter dem Bilde der Panmyelophthise, Ztschr. f. klin. Med. **128**:343, 1935.

214. Rubnitz, A. S.: Atypical Leukemic States and Leukemoid Reactions, Nebraska M. J. **20**:287, 1935.

215. Stasney, J., and Downey, H.: Subacute Lymphatic Leukemia: Histogenetic Study of Case with Three Biopsies, Am. J. Path. **11**:113, 1935.

216. Jackson, H., Jr.: Differential Diagnosis of Agranulocytic Angina from Acute Leukemia, Am. J. M. Sc. **188**:604, 1934.

217. Julliard: Agranulocytose et leucémie monocytes au cours d'une angine nécrotique avec nécrose pulmonaire terminale, Arch. d. mal. du cœur **28**:311, 1935.

218. Kerlin, W. S.: Differential Diagnosis Between Agranulocytic Angina and Acute Leukemia, New Orleans M. & S. J. **87**:759, 1935.

219. Mitchell, E. W., and Ramey, W. O.: Case of Aleukemic Leukemia Simulating Agranulocytosis, J. Med. **15**:602, 1935.

220. Monfort, R.: Aplastic Anemia Blood Picture in Splenic Type of Acute Aleucemic Leucemia, M. Rec. **142**:123, 1935.

221. Reaud, A., and Prado, G.: ¿Agranulocitosis a leucemia mieloblastica? Rev. de med. y cir. de la Habana **40**:456, 1935.

Usseglio and Olivetti;[222] Wells;[223] Ederle and Esche;[224] Goldburgh[225]).

Stephens[226] described a fatal case of acute eosinophilic leukemia in a girl of 17 years. There was evidence of extramedullary production of eosinophils with suppression of adequate production of neutrophils.

Leukemia in Animals.—Furth, Ferris and Reznikoff[227] considered that leukemia in man is essentially the same disease as in mice. The acute and chronic forms, both myelogenous and lymphatic, are neoplastic processes, and like cancer the etiology may be multiple, with intrinsic genetic as well as extrinsic genetic factors.

An authoritative summary of the present knowledge of mammalian leukemia, especially in mice, was presented by Richter and MacDowell.[228]

Furth[229] was able to transmit myeloid leukemia from one mouse to another by inoculation with tissue containing living cells (basophilic myelocytes). Inoculation was successful in almost every mouse after it was treated with roentgen rays. The malignant immature granulocytes may produce systemic diffuse disease or localized tumors (multiple myeloma). Experiments suggest that the transmitting mechanism is not a virus. The author considered that transmissible myeloid leukemia of mice is a neoplasm and that factors in its propagation are (*a*) the resistance of the host, (*b*) the route of entry, (*c*) the character of the malignant cell and (*d*) the inoculating dose. De Marval[211] stated, however, that human leukemia is an infectious process.

Lymphoid and myeloid infiltrations developed in 95 per cent of mice with spontaneous mammary carcinoma. The total irradiation of mice with cancer with small doses of roentgen rays resulted in a more marked increase in the incidence of leukemia than normally occurred in this

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222. Usseglio, G., and Olivetti, R.: Sui rapporti tra leucemie acute e mielosi aplastiche (Nota critica su un caso di linfoadenosi acuta con mielosi globale pseudoaplastica terminale), Minerva med. **1**:183, 1935.

223. Wells, J. J.: Acute Myelogenous Aleukemic Leukemia with Simulated Agranulocytosis: Report of Case, U. S. Nav. M. Bull. **33**:527, 1935.

224. Ederle, W., and Esche, G.: Agranulocytose und Leukämie, Folia haemat. **52**:179, 1934.

225. Goldburgh, H. L.: Aleucemic Leucosis: Report of Case of Myelogenous Leucemia in Aleucemic Phase with a Neutrophilic Angina and Recovery from Latter State, M. Rec. **140**:496, 1934.

226. Stephens, D. J.: Acute Eosinophilic Leukemia, Am. J. M. Sc. **189**:387, 1935.

227. Furth, J.; Ferris, H. W., and Reznikoff, P.: Relation of Leukemia of Animals to Leukemia of Man, J. A. M. A. **105**:1824 (Dec. 7) 1935.

228. Richter, Maurice N., and MacDowell, E. C.: Experiments with Mammalian Leukemia, Physiol. Rev. **15**:509, 1935.

229. Furth, J.: Transmission of Myeloid Leukemia of Mice: Its Relation to Myeloma, J. Exper. Med. **61**:423, 1935.

strain of mice. Observations indicated that hyperplastic myeloid or lymphoid proliferations were transformed into leukemic ones after roentgen irradiation in susceptible mice (Hueper [230]). This is of interest in connection with the report of Kugelmeier [231] of the occurrence of a leukemoid reaction in 2 patients with carcinoma of the stomach and of Schreiner and Wehr [232] on cancer associated with leukemia (see also Paviot, Guichard and Plauchu;[233] Oberling and Guerin [234]). The rôle of heredity in spontaneous mouse lekemia was reported by MacDowell and Richter [235] and by MacDowell, Taylor and Potter.[236] Leukemia coincident with and transmissible by spindle cell sarcoma in mice was reported by Parsons.[237]

MacDowell, Taylor and Potter [238] demonstrated that susceptible mice may be immunized to transplantable leukemia by treatment with small numbers of leukemic cells. Later Rhoads and Miller [239] showed that a similar effect can be produced by the injection of normal lymphoid cells. When malignant cells are injected into immunized subjects, they first proliferate and then undergo degeneration. Immunity to transplantable mouse leukemia is, then, not the result of blockade or invasion of lesions by normal host lymphocytes, as the injected cells are necrotic before the mobilization of host cells takes place (Potter and Findley [240]).

230. Hueper, W. C.: Leukemoid and Leukemic Conditions in White Mice with Spontaneous Mammary Carcinoma, Folia haemat. **52**:167, 1934.

231. Kugelmeier, L. M.: Leukämoide Reaktionen bei Carcinom, Folia haemat. **53**:370, 1935.

232. Schreiner, B. F., and Wehr, W. H.: Cancer Associated with Leukemia, Am. J. Cancer **21**:368, 1934.

233. Paviot, J.; Guichard, A., and Plauchu, M.: Sur une forme particulière de cancer secondaire des os. Les anémies cancéreuses avec myélémie, J. de méd. de Lyon **16**:45, 1935.

234. Oberling, C., and Guerin, M.: Leucémie et cancer: Etude expérimentale. Rev. méd. franç. **15**:755, 1934.

235. MacDowell, E. C., and Richter, M. N.: Mouse Leukemia: Rôle of Heredity in Spontaneous Cases, Arch. Path. **20**:709 (Nov.) 1935.

236. MacDowell, E. C.; Taylor, M. J., and Potter, J. S.: Dependence of Protection Against Transplantable Mouse Leukemia upon Genetic Constitution of Immunizing Tissue, Proc. Nat. Acad. Sc. **21**:507, 1935.

237. Parsons, L. D.: Leukaemia Coincident with and Transmissible by Spindle-Celled Sarcoma in Mouse, J. Path. & Bact. **40**:45, 1935.

238. MacDowell, E. C.; Taylor, M. J., and Potter, J. S.: Immunization of Mice Naturally Susceptible to Transplantable Leukemia, Proc. Soc. Exper. Biol. & Med. **32**:84, 1934.

239. Rhoads, C. P., and Miller, D. K.: Induced Resistance to Transmissible Leukemia in Mice, Proc. Soc. Exper. Biol. & Med. **32**:817, 1935.

240. Potter, J. S., and Findley, M. D.: Histological Observations on Resistance to Transplantable Leukemia in Immunized Mice, Proc. Soc. Exper. Biol. & Med. **32**:1338, 1935.

The subject of leukemia and lymphomatoses in fowls has received much study (Stubbs and Furth;[241] Furth;[242] Engelbreth-Holm;[243] Engelbreth-Holm and Meyer;[244] Engelbreth-Holm, Meyer and Uhl;[245] Meyer, Engelbreth-Holm and Uhl;[246] Wallbach[247]).

The virus of chicken leukosis (strain 2) produces a neoplastic growth of lymphocytes but does not produce a tumor at the site of injection when given intramuscularly. Two transmissible strains of the virus of neurolymphomatosis have been isolated; one produces no blood changes or "erythroleukosis" with myeloblastic leukemia, and the other, anemia with an increase in the number of large lymphocytes and occasionally myelocytes (Furth[248]). The transmitting agent is inactivated by freezing at —30 C. for thirty minutes or by drying from the frozen state.

Bernard[249] produced a leukemoid condition and a tumor of the bone by intramedullary injections of tar into apes.

Monocytic Leukemia.—Mann[250] reported that splenomegaly and generalized lymphadenopathy may be present in only half of the cases of monocytic leukemia. At first there is a period of a few months in which infection, progressive pallor and lassitude are the most marked features. This is followed by ulcerative stomatitis and ulceration of the gums, local lymphadenopathy and rapid deterioration of the patient. With

241. Stubbs, E. L., and Furth, J.: Relation of Leucosis to Sarcoma of Chickens: Sarcoma and Erythroleukosis (Strain 13), J. Exper. Med. **61**:593, 1935.

242. Furth, J.: Studies on Effect of Roentgen Rays on Lymphomatosis of Mice, Am. J. Roentgenol. **32**:377, 1934.

243. Engelbreth-Holm, J.: Experimental Studies on Transplantable Leukosis of Fowl, Bibliot. f. læger **127**:119, 1935.

244. Engelbreth-Holm, J., and Meyer, A. R.: Variation in Percentage of Takes in Three Strains of Chicken Leukosis, Acta path. et microbiol. Scandinav. **12**:366, 1935.

245. Engelbreth-Holm, J.; Meyer, A. R., and Uhl, E.: On Chemotherapy in Leucosis of Fowls, Acta path. et microbiol. Scandinav. **12**:491, 1935.

246. Meyer, A. Rothe; Engelbreth-Holm, J., and Uhl, E.: Further Studies on Agent of Chicken Leukosis, Acta path. et microbiol. Scandinav. **12**:378, 1935.

247. Wallbach, G.: Recherches sur la leucémie des poules: Variation de la symptomatologie selon les modifications expérimentales du virus, Sang **9**:445, 1935; Recherches sur la leucémie des poules: Retentissement sur l'organisme de modifications apportées aux facteurs expérimentaux, ibid. **9**:553, 1935; Recherches sur la leucémie des poules: Les formes atypiques de la leucémie des poules, ibid. **9**:566, 1935.

248. Furth, J.: Lymphomatosis in Relation to Fowl Paralysis, Arch. Path. **20**:379 (Sept.) 1935.

249. Bernard, J.: Etat leucémoïde et tuméfaction osseuse provoqués chez le singe par les injections intramédullares de goudron, Sang **9**:790, 1935.

250. Mann, W. N.: Case of Monocytic Leukemia, Guy's Hosp. Rep. **85**:178, 1935.

this a leukemic blood picture develops, with many mature monocytes as well as immature forms.

Mitchell [251] presented the report of a case of malignant monoblastoma, as a variant of monocytic leukemia, and reviewed the reports of 42 cases in the literature. The patient described had an aleukemic and a leukemic phase. There were multiple recurring monoblastomas which were formed by localized hyperplasia of the histiocytes of the diffuse connective tissues. Mercer [252] found a diffuse exanthematous eruption in 2 cases of monocytic leukemia. The lesions were slightly red macules and papules, changing to slate blue, and firmer pale papules deeper in the skin. Many of the lesions were transient, but some become necrotic.

Whitby and Christie [253] described the case of a patient with acute monocytic leukemia in which there were two remissions. The anemia was out of proportion to the apparent degree of the leukemic process. The necrotic lesions in the mouth were more on the alimentary mucous membranes than on the respiratory part of the pharynx, the ulceration not involving the tonsil or the nasal mucous membrane. During much of the course there was granulopenia. Hepatomegaly accompanied the appearance of a frankly leukemic blood picture, without enlargement of the spleen and lymph nodes. Studies of the spleen did not show evidence of proliferation of reticulum cells or of desquamation of histiocytes into the blood.

In a case of monocytic leukemia described by Haining, Kimball and Janes,[254] a leukemic mass in the rectal wall produced complete intestinal obstruction simulating carcinoma of the rectal wall. The authors considered monocytic leukemia as a sinus reticulosis and myelogenous and lymphatic leukemia as a true reticulosis.

Kracke and Garver [255] discussed the present views on leukemia. They stated that the chief cell type in monocytic leukemia has its origin in the bone marrow, and this theory is presented as evidence that monocytic leukemia is an atypical phase of myelogenous leukemia.

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251. Mitchell, Louis A.: Malignant Monoblastoma: A Variant of Monocytic Leukemia, Ann. Int. Med. **8**:1387, 1935.

252. Mercer, S. T.: Dermatosis of Monocytic Leukemia, Arch. Dermat. & Syph. **31**:615 (May) 1935.

253. Whitby, L. E. H., and Christie, J. M.: Monocytic Leukaemia, Lancet **1**:80, 1935.

254. Haining, R. B.; Kimball, T. S., and Janes, O. W.: Leukemic Sinus Reticulosis (Monocytic Leukemia) with Intestinal Obstruction: Report of Case with Partial Autopsy, Arch. Int. Med. **55**:574 (April) 1935.

255. Kracke, R. R., and Garver, H.: Differential Diagnosis of Leukemic States, with Particular Reference to Immature Cell Types, J. A. M. A. **104**:697 (March 2) 1935.

Details of cutaneous eruptions in chronic cases of lymphatic leukemia (Miyamoto and Shikuma [256]) and of other forms (Saslawsky and Ioffe [257]) have been described.

Treatment.—Various forms of roentgen therapy have been evaluated. Langer,[109] basing his treatment on the hypothesis that leukemia is the result of overactivity of the sympathetic nervous system, advocated roentgen therapy over the paravertebral ganglions (spinal column). The principles and technic of irradiation have been studied by Nisbet,[110] Pohle,[258] Rosselli del Turco,[259] Erickson and Dittmer,[260] Feuerstein [261] and Huguet.[262]

High voltage roentgen ray therapy combined with lead therapy was tried by Schmahl.[263] Arzt [264] uses radium therapy.

Kalapos [265] studied the effect of the administration of benzene in cases of leukemia, and Krebs and Clemmesen [266] reported on the use of lead compounds. Lucia [267] used a 1 per cent solution of antimony and potassium tartrate in sterile distilled water intravenously in progressive graded doses of 2, 3 and 5 cc. on alternate days. There was a marked reduction in the number of white blood cells in 6 of 9 patients with chronic myelogenous, chronic lymphatic and advanced monocytic

256. Miyamoto, Y., and Shikuma, K.: Ueber einen Fall von chronischer lymphatischer Leukämie mit einen selten beobachten Hautsymptome, Nagasaki Igakkwai Zassi **13**:814, 1935.

257. Saslawsky, A., and Ioffe, E.: Skin Eruptions in Leukemia, Urol. & Cutan. Rev. **39**:331, 1935.

258. Pohle, E. A.: Radiation Therapy in Medical Practice: Leukemia, Hodgkin's Granuloma and Allied Diseases, Wisconsin M. J. **34**:632, 1935.

259. Rosselli del Turco, L.: Il meccanismo di azione dei raggi röntgen sull'emopoiesi, in rapporto ad una eventuale terapia chimica delle leucemia, Riv. di clin. med. **35**:863, 1934.

260. Ericksen, L. G., and Dittmer, M. G.: X-Ray Therapy in Leukemia, J. Iowa M. Soc. **25**:553, 1935.

261. Feuerstein, B. L.: Radiation in Leucemia: Report of Seventy-Seven Cases so Treated, M. Rec. **140**:492, 1934.

262. Huguet: De l'influence des rayons X sur le nombre des globules rouges dans les leucémies, Marseille méd. **2**:684, 1934.

263. Schmahl, P. J. R.: Myelogenous Leukemia, J. Am. Inst. Homeop. **28**:75, 1935.

264. Arzt, L.: Das Radium in der Therapie der Leukämien, Wien. klin. Wchnschr. **48**:166, 1935.

265. Kalapos, I.: Die Wirkung des Benzols bei der Leukämie, Klin. Wchnschr. **14**:864, 1935.

266. Krebs, C., and Clemmesen, J.: Die Bleiverbindungen R232 und R237b verwendet bei der experimentellen Therapie von Tumoren und Leukose, Ztschr. f. Krebsforsch. **41**:260, 1934.

267. Lucia, S. P.: Effects of Tartar Emetic on Leukocyte Count, Proc. Soc. Exper. Biol. & Med. **32**:1109, 1935.

leukemia, Hodgkin's disease and eosinophilic leukocytosis. The size of the lymph nodes and spleen, however, was not affected.

Desjardins [268] has summarized the present status of the treatment of leukemia as follows:

> In acute leukemia, exposure to roentgen rays or radium is seldom followed by perceptible improvement, and experienced radiologists usually do not encourage such treatment. In the subacute form cautious treatment, and in the chronic form thorough treatment, yield more or less marked improvement for periods varying from months to several years. Usually the treatment must be repeated from time to time, depending on the numerical behavior of the leukocytes and on the tendency of the spleen or lymph nodes to enlarge. Effective treatment can be given with roentgen rays or radium. At the outset, and when extensive areas require irradiation, roentgen rays are preferable.
>
> In myeloid leukemia the rays are directed first to the spleen, and then, if this is not sufficient to reduce the number of leukocytes approximately to the normal level, the mediastinum and long bones also may be irradiated. When the spleen is large, the surface of the abdomen corresponding to that organ may be divided into a number of fields, approximately 10 cm. square, and each field should be exposed to a moderate dose of roentgen rays. If radium is used to irradiate the enlarged spleen, a large pack is required. The effect of treatment on the leukocytes should be followed closely by daily or frequent blood counts. When the number of leukocytes diminishes rapidly, the number of fields irradiated each day should be correspondingly reduced; otherwise, an excessive leukopenia may result. An abnormally small number of erythrocytes at the outset need not be regarded as a contraindication; under treatment the number of these cells tends to increase as the number of leukocytes diminishes. After a patient has been treated a number of times at intervals of months, the effectiveness of treatment tends to diminish; but this varies considerably from patient to patient. If the patient cooperates faithfully, the disease may often be kept under control for prolonged periods, sometimes for many years.
>
> In lymphoid leukemia the treatment is directed first to the main groups of lymph nodes in the neck, axillae and groins, as well as to the mediastinal and retroperitoneal lymph nodes. If, by the time these several regions have been irradiated, the number of leukocytes has not diminished sufficiently, additional treatment to the shaft of the major long bones may have to be given.

Splenectomy has been resorted to by some (de Marval and Bomchil; [269] de Marval, Simonetti and Bomchil; [270] Becker [271]), but Rosenthal and Harris [272] advised against it. The value of transfusions of blood, the administration of arsenic and roentgen irradiation was

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268. Desjardins, A. U.: Radiotherapy (Roentgen Rays; Radium), J. A. M. A. **105**:2152 (Dec. 28) 1935.

269. de Marval, L., and Bomchil, G.: Esplenectomía en la leucemia, Semana méd. **1**:1289, 1935.

270. de Marval, L.; Simonetti, C., and Bomchil, G.: Esplenectomía en la leucemia, Semana méd. **2**:261, 1935.

271. Becker, A.: Milzextirpation bei Leukämie, Zentralbl. f. Chir. **62**:1461, 1935.

272. Rosenthal, N., and Harris, W.: Leukemia: Its Diagnosis and Treatment, J. A. M. A. **104**:702 (March 2) 1935.

reiterated. In cases of leukopenia radiotherapy is of no value in reducing the size of the spleen and is contraindicated in cases of severe leukopenia as it may be followed by secondary infection, necrosis and hemorrhage. Arsenic may be employed advantageously between roentgen treatment. The authors stated that irradiation is justifiable and useful in the treatment of acute leukemia, but they advised that transfusions of blood also be given.

In a case of myelogenous leukemia and intraperitoneal hemorrhage, the spleen was removed. A remission of several months followed, and in subsequent relapses roentgen irradiation was employed. Death occurred fifteen months after splenectomy from strangulation ileus. The case reported by Popper [273] illustrates the fact that splenectomy may be performed when an emergency requires it but that the course of the disease is not grossly influenced by the procedure.

Israëls [274] did not note beneficial effects of iodine, such as Friedgood had obtained, in 5 cases of chronic lymphatic leukemia. He did note a moderate improvement in the white blood cell count, which he attributed to the direct action of iodine on the leukocytes and not on any fundamental leukemic mechanism. He therefore does not see any evidence to justify thyroidectomy in this disease.

In an effort to see if the deficiency of certain substances was the cause of chronic myelogenous leukemia, Castle, Meyer and Chew [275] tried desiccated mucosa of the stomach and small intestine, desiccated hog pancreas and mixtures of most of the fresh organs of newly born rabbits, with no improvement in the condition of the patients. Daily transfusions of the plasma or whole blood of normal persons was not effective.

INFECTIOUS MONONUCLEOSIS

In 1885 Filatow originally described an idiopathic lymphadenopathy. Pfeiffer in 1889 commented on an acute disease occurring in children, characterized by fever, enlargement of glands and changes in the blood, and called it glandular fever. Desplats in 1894 noted the involvement of the axillary and inguinal glands as well as of the glands in the cervical region. In the same year Hörschelmann observed a scarlatina-like eruption during the course of the disease. West first described the disease in the United States in 1896, and Williams originally described it in England in 1897. Sprunt and Evans in 1920 and Longcope in 1922

273. Popper, H. L.: Splenektomie bei Leukämie, Med. Klin. **31**:615, 1935.

274. Israëls, M. C. G.: Treatment of Lymphatic Leukaemia with Special Reference to Use of Iodine, Brit. M. J. **1**:1021, 1935.

275. Castle, W. B.; Meyer, O. O., and Chew, W. B.: Negative Results of Treatment of Chronic Myelogenous Leukemia as a Deficiency Disease, Proc. Soc. Exper. Biol. & Med. **32**:660, 1935.

established the disease on a more secure clinical basis and termed it "infectious lymphocytosis" and "infectious mononucleosis," respectively. Most accurate and detailed descriptions of the changes in the blood were made by Downey and McKinlay in 1923.

Various organisms have been isolated and described [276] as the etiologic factor of infectious mononucleosis, but none of them has ever been confirmed by others than the original investigators. Sporadic and epidemic cases have been observed in Europe, North America, China, Australia and the Falkland Islands, but only 3 cases have been noted in the Tropics. Apparently the disease occurs in either sex and at any age, though it is more common in children and in persons under 40. The prodromal period varies, depending on the type of disease. [276a] In the glandular type, the prodromal period is from one to four days, and in the angiose type, from one to three weeks. The period of incubation is described by some as from seven to eight days. [276d]

The more common symptoms, as observed by various clinicians, [277] are headache, general malaise, sore throat, tenderness of the glands, backache, chilliness, anorexia, coryza, sweating, weakness, cough, dizziness, sore bleeding gums, nausea, stiff neck, epistaxis, stomatitis, abdominal pain, rash, photophobia and conjunctivitis. The physical signs usually encountered are fever, enlargement and tenderness of the glands, injection of the throat, enlargement of the spleen, enlargement of the tonsils, membranous angina and a maculopapular rash. The temperature usually varies between 101 and 105 F. Enlargement of the glands is present in 100 per cent of the cases and tenderness in 76 per cent. Suppuration of the glands has seldom been observed.

The complications which are encountered are variable: sepsis, hematuria, purpura, jaundice, appendicitis, meningismus and involvement of the respiratory tract.

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276. (*a*) Tidy, H. L.: Glandular Fever and Infectious Mononucleosis (Lumleian Lecture), Lancet **2**:180, 1934. (*b*) Baldridge, C. W.; Rohner, F. J., and Hansmann, G. H.: Glandular Fever (Infectious Mononucleosis), Arch. Int. Med. **38**:413 (Oct.) 1926. (*c*) Sprunt, T. P.: Infectious Mononucleosis (Glandular Fever), Internat. Clin. **3**:92, 1933. (*d*) McKinlay, C. A.: Infectious Mononucleosis: I. Clinical Aspects, J. A. M. A. **105**:761 (Sept. 7) 1935. (*e*) Nyfeldt, A.: Etiologie de la mononucléose infectieuse, Compt. rend. Soc. de biol. **101**:590, 1929. (*f*) Gorham, L. W.; Smith, D. T., and Hunt, H. D.: The Experimental Reproduction of the Blood Picture of Infectious Mononucleosis in the Guinea Pig, J. Clin. Investigation **7**:504, 1929.

277. (*a*) Stuart, C. A.; Burgess, A. M.; Lawson, H. A., and Wellman, H. E.: Some Cytologic and Serologic Aspects of Infectious Mononucleosis, Arch. Int. Med. **54**:199 (Aug.) 1934. (*b*) Downey, H., and Stasney, J.: Infectious Mononucleosis: II. Hematologic Studies, J. A. M. A. **105**:764 (Sept. 7) 1935. (*c*) Baldridge.[276b] (*d*) Sprunt.[276c] (*e*) McKinlay.[276d]

Leukocytosis,[278] of varying degree, is present at some time during the course of the disease; leukopenia may occur at the onset. The usual white cell count is from 15,000 to 20,000 cells per cubic millimeter. The red blood cell count and the hemoglobin content are within normal limits. The exact classification of the atypical mononuclear cells observed is a difficult task. They have been accurately described by many authors.[279] It is generally accepted that they are of the lymphocytic series, though this view has many opponents.

Biopsy[280] of the glands involved reveals a rather characteristic picture. Grossly, the glands are of variable size, soft and spongy, with a distended white capsule. The normal architecture is obliterated. The lymphoid tissue as well as the reticulum is hyperplastic. The sinuses are compressed. The irregularity of the hyperplasia of the reticulum and lymphoid tissue gives the gland a characteristic nodular and spotty appearance.

The prognosis is very good, though relapses and remissions are not uncommon. Apparently the disease is self-limited. The course may be protracted, and both glandular and hematopoietic changes may persist for many months.

The diagnosis can be made usually by the presence of the painful glands and the characteristic changes in the blood. Recently, Paul and Bunnell[281] devised a heterophilic antibody test which appears to be practically specific for infectious mononucleosis (serum sickness to be excluded). This work has been confirmed by many investigators,[282]

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278. Baldridge.[276b] McKinlay.[276d] Downey and Stasney.[277b]

279. Cady, L. D.: The Diagnosis of Sporadic Infectious Mononucleosis (Glandular Fever), Am. J. M. Sc. **175**:527, 1928. Osgood, E. E.: Fenestration of Nuclei of Lymphocytes: A New Diagnostic Sign in Infectious Mononucleosis, Proc. Soc. Exper. Biol. & Med. **33**:218, 1935. Baldridge.[276b] Stuart, Burgess, Lawson and Wellman.[277a] Downey and Stasney.[277b]

280. Baldridge.[276b] Downey and Stasney.[277b]

281. Paul, J. R., and Bunnell, W. W.: The Presence of Heterophile Antibodies in Infectious Mononucleosis, Am. J. M. Sc. **183**:90, 1932.

282. (*a*) Bunnell, W. W.: A Diagnostic Test for Infectious Mononucleosis, Am. J. M. Sc. **186**:346, 1933. (*b*) Bailey, G. H., and Raffel, S.: Hemolytic Antibodies for Sheep and Ox Erythrocytes in Infectious Mononucleosis, J. Clin. Investigation **14**:228, 1935. (*c*) Boveri, R.: Ueber das Vorkommen heterophiler Antikörper bei lymphoidzelliger Angina, Klin. Wchnschr. **12**:666, 1933. (*d*) Rosenthal, N., and Wenkebach, G.: Die Bedeutung der heterophilen Antikörperreaktion für die Diagnose der infektiösen Mononucleose, ibid. **12**:499, 1933. (*e*) Van Ravenswaay, A. C.: The Heterophile Agglutination Test in the Diagnosis of Infectious Mononucleosis, New England J. Med. **211**:1001, 1934. (*f*) Davidsohn, I.: Infectious Mononucleosis, Am. J. Dis. Child. **49**:1222 (May) 1935. (*g*) Bernstein, A.: Antibody Responses in Infectious Mononucleosis, J. Clin. Investigation **13**:419, 1934. (*h*) Butt, E. M., and Foord, A. G.: The Heterophile Antibody Reaction in the Diagnosis of Infectious Mononucleosis, J. Lab. & Clin. Med. **20**:538, 1935.

although there is considerable difference of opinion as to the nature of the antibodies [283] involved in the reaction.

There is no specific treatment for this malady. Rest in bed, forcing of fluids and a high caloric diet are indicated.

AGRANULOCYTIC ANGINA

The following important aspects of this disease have been emphasized during the past year: (1) the importance of various drugs, especially aminopyrine, from an etiologic standpoint, (2) a more careful study of the pathologic process in the bone marrow, (3) attempts to produce the disease experimentally and (4) the value of various types of treatment.

Etiology.—Kracke and Parker [284] have written the most comprehensive article on the etiology of agranulocytic anemia. Their article includes a most complete and satisfactory summary of the knowledge with an extensive bibliography of the subject. They emphasized the facts that the disease occurred rarely before 1922, that it appears more frequently in women of middle age, that it is uncommon in Negroes and that it has its greatest incidence in persons of a social status above the average. In addition, they stated that it occurs most frequently in persons of the medical group and in countries, such as Germany and the United States, which "have become flooded with various synthetic drugs." All of these statements may be interpreted as suggestive evidence that a drug, such as aminopyrine, may be an important factor in causation of the disease. These authors concluded that a great deal of evidence has been accumulated which indicates that the administration of aminopyrine alone or in combination with one of the barbiturates is responsible for the disease in a large number of patients.

Kracke and Parker [284] emphasized, correctly, that it is almost impossible to obtain an accurate history as to the ingestion of drugs after a patient is dead, regardless of all statements of the immediate family and the attending physician. They cited examples which illustrate how difficult it may be to secure a reliable history even from a living patient and concluded that a "negative drug history is often a worthless one." While it is not claimed that all patients with agranulocytic angina have taken

283. Stuart, C. A.: Heterophile Antibodies in Infectious Mononucleosis, Proc. Soc. Exper. Biol. & Med. **32**:861, 1935. Davidsohn, I., and Walker, P. H.: The Nature of the Heterophilic Antibodies in Infectious Mononucleosis, Am. J. Clin. Path. **5**:455, 1935. Paul and Bunnell.[281] Bailey and Raffel.[282b]

284. Kracke, R. R., and Parker, F. P.: The Relationship of Drug Therapy to Agranulocytosis, J. A. M. A. **105**:960 (Sept. 21) 1935; Correction, ibid. **105**: 1047 (Sept. 28) 1935.

aminopyrine, the foregoing statements may explain why some patients with agranulocytic angina are reported as not having taken the drug.

Gordon [285] is not in accord with the more prevalent view that aminopyrine is an important factor in the production of agranulocytic angina. After questioning 59 of his patients, he concluded that in only 1 case could any therapeutic agent have been related to the etiology of the disease. In his opinion a number of factors may be responsible for the disease, but he considered that its absolute etiology is still unknown.

Jackson [286] stated that aminopyrine has an important etiologic significance in some cases, but he expressed the opinion that conclusive evidence has not demonstrated that it is the sole or even the major cause of the disease. In urging that caution be used in accepting this drug as an important cause of the agranulocytic state, he stated, in regard to its etiologic relationship to the disease, that some patients recover even though the aminopyrine therapy is continued and that in other patients there is no evidence to indicate that the drug was taken prior to the attack. He has observed patients who took aminopyrine and became ill with the disease, but despite the fact that the drug was discontinued one or more relapses occurred. In other patients, in whom the attack was precipitated by aminopyrine, there has been no evidence that after recovery they continue to be sensitive to it. This is evident as increasing doses have not produced a significant change in the blood picture. It has been stated that the incidence of the disease is becoming less, and this has been attributed to the withdrawal of the drug from the market. Yet the evidence indicates that the sales of this preparation had actually increased in the six months prior to the time Jackson's article was written.

Squier and Madison [287] reiterated their opinion that aminopyrine is a "frequent" etiologic factor in the production of the disease, as indicated in their previous paper, in which it was reported that 19 of their 20 patients had taken the drug directly before the onset of the condition. They presented observations on 2 patients which showed the effect on the granulocytes of the peripheral blood of 10 grains (0.65 Gm.) of amytal compound (amytal with aminopyrine), 5 grains (0.324 Gm.) of aminopyrine alone and the application of a 10 per cent solution of the latter drug to the unbroken skin. A significant granulopenia developed following the administration of the foregoing drugs, but there was no important change in the white blood cell count when amytal alone was

285. Gordon, W. H.: Malignant Neutropenia: Its Etiology and Treatment, J. Michigan M. Soc. **34**:7, 1935.

286. Jackson, H., Jr.: Agranulocytosis, Ann. Int. Med. **9**:26, 1935.

287. Squier, T. L., and Madison, F. W.: Drug Hypersensitivity as Cause of Acute Primary Granulocytopenia, Wisconsin M. J. **34**:175, 1935.

given. They concluded that the cause of the disease is an allergic response to certain drugs rather than a heightened pharmaceutic or physiologic response.

Kastlin [288] and also Jackson [286] have made observations which indicate that there must be a variability of susceptibility in "sensitive" persons if aminopyrine plays an important etiologic rôle in this disease. The former reported the case of a patient who had taken aminopyrine for years on account of insomnia. Marked granulopenia developed (800 white blood cells per cubic millimeter), but recovery followed despite the daily administration of amytal and aminopyrine and of an allylioso-propyl barbituric acid with aminopyrine. With a recurrence of the granulopenia these drugs were withheld. After a temporary recovery the disease again progressed and terminated fatally.

Limarzi and Murphy [289] reported the case of a young woman who had five recurring attacks of agranulocytosis over a period of about two and one-half years. She had taken from 15 to 20 grains (1 to 1.3 Gm.) of aminopyrine, with or without acetylsalicylic acid, each week for the last four years and yet showed no clinical evidence of agranulocytosis in the interim between the five attacks. Furthermore, during the last attack, at which time the leukocyte count fell to 1,700 per cubic millimeter, with 12 per cent polymorphonuclear neutrophils, a total of 370 grains (24 Gm.) of aminopyrine was given. Despite this, the blood returned to normal, and the patient made a complete recovery. From this report and the others cited here, it is strongly suggested that if the condition is due to a susceptibility or idiosyncrasy to aminopyrine the degree must vary widely.

Stephens and Lawrence [290] observed a patient with recurrent attacks of agranulocytosis which occurred in association with the menstrual periods. Cyclic recurrences were present for one year after subtotal hysterectomy and bilateral salpingo-oophorectomy were done. At the end of this time administration of all drugs except codeine was omitted, and no further attacks occurred in the remaining ten months during which the patient was observed. Prior to the time of omission of the drugs, the patient had taken an unknown amount of aminopyrine. It was probably a considerable amount, as the patient had frequent migraine headaches and dysmenorrhea, for which she took aminopyrine,

288. Kastlin, G. J.: Primary Granulocytopenia, Pennsylvania M. J. **38**:600, 1935.

289. Limarzi, L. R., and Murphy, I. G.: Amidopyrine and Granulopenia: Reappearance of Granulocytosis in Cases of Recurring Agranulocytosis After Large Doses of Amidopyrine; Clinical Experiment, J. Lab. & Clin. Med. **20**:616, 1935.

290. Stephens, D. J., and Lawrence, J. S.: Cyclical Agranulocytic Angina, Ann. Int. Med. **9**:31, 1935.

acetylsalicylic acid and sodium amytal. The authors were unable to state if the omission of the aminopyrine was responsible for the disappearance of the recurrences.

Pathology of the Bone Marrow.—Custer,[291] after a study of 11 cases, concluded that the histopathologic picture of the bone marrow is fairly constant. He attributed the previous inconsistent reports to (1) failure to examine the marrow from more than one site in the body and to (2) faulty technic, which makes accurate cell identification impossible. According to him, the marrow shows a striking proliferative activity of the myeloblasts. This is in contrast to the marrow of a normal person, in which the predominating cells of the granulocyte series are promyelocytes and myelocytes. Myeloblasts are rarely present. Custer considered that there is a failure of the myeloblasts to maturate and that this is due to a lack of intrinsic maturation factor or the action of an extrinsic chemical or bacterial toxin. This observer furthermore stated that there is a difference between the marrow of persons with idiopathic agranulocytosis and that of persons with arsenical or septic neutropenia, as in the latter conditions the granular forms of the neutrophil series predominate.

Attempts to Produce the Disease Experimentally.—Despite various attempts, it cannot be said that it is possible to produce true agranulocytosis in animals. This is not surprising if it is agreed that the condition occurs only in certain persons who are susceptible. If this is true one would not expect the disease to develop after the administration of aminopyrine or another drug unless the animal had a spontaneous sensitivity to it, or unless this state could be artificially induced.

Stenn [292] reported that he was unable to produce the disease in guinea-pigs, rabbits or monkeys when aminopyrine was given orally, subcutaneously, intraperitoneally and intravenously. He also was unable to produce the disease when the drug was injected into animals in which an attempt had been made to sensitize them to it. There was no evidence that aminopyrine could produce the disease in animals under the following circumstances: (1) when there was severe anemia as a result of bleeding; (2) after the bone marrow had been previously injured by the administration of benzene in olive oil; (3) after the animals had been infected for one month with Bacillus subtilis, Streptococcus viridans and Salmonella suipestifer, and (4) after a complete fast of five days.

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291. Custer, R. P.: Studies on the Structure and Function of Bone Marrow: Bone Marrow in Agranulocytosis, Am. J. M. Sc. **189**:507, 1935.

292. Stenn, F.: Etiologic Relationship of Amidopyrine to Agranulocytosis, J. Lab. & Clin. Med. **20**:1150, 1935.

Kunde and his co-workers [293] were unable to produce granulopenia when from 1 to 4 tablets of cibalgin (aminopyrine [dimethylamino-phenyl-di-methylpyrazolone] and dial [diallylmalonylurea]) were given to rabbits for seventeen consecutive days. These drugs failed to prevent the leukocytosis which occurs in rabbits with sniffles or a "certain gastro-intestinal infection." Rabbits in which the thyroid gland had been removed six weeks previously were given cibalgin, and leukocytosis developed in response to the infection which was comparable to that which occurred in rabbits with intact thyroids.

Smith and Mack [294] gave 0.75 Gm. each of amytal and aminopyrine to 60 day old rats which had been placed on the following deficient diet: commercial casein, 18 per cent; corn starch, 54 per cent; butter fat, 18 per cent; lard, 6 per cent, and the Osborne-Mendel salt mixture, 4 per cent. The white blood cell counts of the animals were reduced 50 per cent, although there was no significant reduction in the number of granulocytes. There was continuous hematuria after the experiment had been in progress for a few days. A control group of rats which received a deficient diet alone did not show a reduction in the white blood cell count.

Climenko [295] studied the inhibiting effect of aminopyrine, antipyrine, alpha-di-nitrophenol, phenylhydrazine hydrochloride, catechol and ortho-quinone on the leukocytosis which is ordinarily produced in the rabbit by the parenteral injection of nucleic acid. He reported detailed observations on 1 animal which were typical of the results on 7 others. The intramuscular injection of 5 mg. of nucleic acid per kilogram of body weight produced a maximum white blood cell count of 15,100 in four hours, 34 per cent of the cells being polymorphonuclear neutrophils. After the animal received 0.2 Gm. of aminopyrine orally for eighteen days, a similar dose of nucleic acid was given intramuscularly. No significant response was evoked in the white blood cell count. Similar inhibitions were produced following the administration of the other drugs previously mentioned.

Bolton [296] reported the effects of aminopyrine, barbital, aminopyrine and barbital, phenylhydrazine and benzene on the cellular elements of

293. Kunde, M. M.; Herwick, R. P.; Learner, A., and Sternback, M.: Non-Production of Granulocytopenia with an Amidopyrine Compound (Cibalgin) in Some Acute Infections, Proc. Soc. Exper. Biol. & Med. **32**:1121, 1935.

294. Smith, E., and Mack, L.: Effect of Deficient Diet, Amytal and Amidopyrine on Blood Picture of Albino Rat, Proc. Soc. Exper. Biol. & Med. **32**:1623, 1935.

295. Climenko, D. R.: Inhibition of Leukogenic Activity in the Rabbit by Certain Cyclic Compounds, Proc. Soc. Exper. Biol. & Med. **32**:823, 1935.

296. Bolton, V. L.: Laboratory Study of Amidopyrine, Barbital, Phenyl Hydrazine and Benzene in Relation to Agranulocytic Angina, J. Lab. & Clin. Med. **20**:1199, 1935.

blood of normal dogs. Of the 6 animals which were observed, there was a moderate drop in the leukocyte count in only 1 animal which received aminopyrine and 1 which received benzene. As there were no significant changes in the percentage of granulocytes, it cannot be said that a blood picture similar to that observed in agranulocytic angina had been produced. The author suggested that possibly the granulopenia of agranulocytic angina is due to transformation products of certain drugs which may in susceptible subjects cause arrested maturation of the myeloid elements of the bone marrow.

Zia and Forkner [297] noted that acute granulopenia occurred in 8 of the 71 patients with visceral leishmaniasis whom they observed. This was more than an intensification of the already existing leukopenia, as the polymorphonuclear neutrophils either abruptly decreased or completely disappeared from the peripheral blood. The condition developed in 6 of these patients when they were undergoing treatment with urea stibamine (carbamide salt of p-amino-phenyl stibonic acid containing antimony in the pentavalent form) or neostibosan (p-amino-phenyl-stibinate of di-ethylamine, containing antimony in the pentavalent form).

These preparations were given intravenously to determine their effect on the blood of normal rabbits. Repeated injections of large amounts did not cause the picture of acute agranulocytic angina in the peripheral blood.

Harris and Schattenberg [298] studied the effect on experimental animals of the subcutaneous, intraperitoneal and intracardiac injection of B. enteritidis, B. Welchii and Str. haemolyticus and toxic products derived from these bacteria. The toxic material was prepared from the exudate obtained from guinea-pigs with fatal peritonitis which was induced by these organisms and was then passed through a Berkefeld or Seitz-Wertz filter. When this was injected parenterally into guinea-pigs, granulopenia was induced. The authors concluded that there is some doubt as to whether this condition resembles a true reproduction of the human disease. They concluded also that these experiments indicate that agranulocytic angina is due to varied causes.

Treatment of Agranulocytosis.—Nonspecific therapy, stimulating doses of roentgen rays, liver extract, adenine sulfate, pentnucleotide, blood transfusions and leukocytic cream have been used as therapeutic

297. Zia, L. S., and Forkner, C. E.: Acute Agranulocytosis of Kala-Azar: Negative Effect of Urea Stibamine and Neostibosan (Antimony Preparations) on Blood of Normal Rabbits, Proc. Soc. Exper. Biol. & Med. **32**:536, 1934.

298. Harris, W. H., and Schattenberg, H. J.: Experimental Studies in So-Called Agranulocytic Angina: Effects of Toxic Products of Certain Bacteria Recovered from Stool and Blood of Human Being upon Leukocytes of Animals. J. Lab. & Clin. Med. **20**:1053, 1935.

agents in this disease. Although the administration of pentnucleotide has been used more than the other forms of treatment, it cannot be said that there is a general agreement concerning its value. Jackson [286] suggested the following possible explanations of why some unfavorable results have been reported: Less than 40 cc. daily, which is the recommended dose, has been given. Unfortunately this dose may cause such severe reactions in some patients that it cannot be tolerated. Complete absence of granulocytes in the peripheral blood is incompatible with life. Despite an adequate dosage, therefore, the patient may die before the beneficial result occurs. The diagnosis of agranulocytosis may be incorrect, and the patient have some other disease such as leukemia.

According to Jackson, [286] if the patient has agranulocytosis anemia should not be present unless it is due to some unrelated disease; nor should there be thrombopenia, purpura or notable enlargement of the spleen; immature white blood cells should be absent from the peripheral blood, and there should be no lymphadenopathy except that which is due to the adjacent sepsis. He expressed the opinion that at present a larger number of patients have recovered after therapy with pentnucleotide than have survived after any other form of treatment. Injections of sterile milk, the use of leukocytic cream and roentgen therapy were considered useless. He is "decidedly" against transfusions of blood because there is no convincing evidence that they are beneficial, and in some instances the white blood cell count may fall following them. He stated that a few patients have been successfully treated with liver extract but that at present its ultimate value cannot be estimated.

He condemned sepsis as a therapeutic agent as there is no evidence that it can stimulate a paralyzed bone marrow.

He stated that the most effective therapy for the disease at present is as follows: (1) intelligent nursing care, (2) adequate fluids and food, (3) careful avoidance of sepsis, (4) administration of full doses of pentnucleotide, (5) the fearless use of such surgical measures as would be instituted in a person with a normal blood and (6) the use of codeine as a sedative.

Several observers have stated that pentnucleotide is the most hopeful remedy for the disease, although their results are not conclusive as the number of patients treated was small in each instance. [299]

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299. Castleden, L. I. M.: Agranulocytic Angina: Fatal Case Treated with Pentnucleotide, Lancet **1**:206, 1935. Fettes, J., and Whitby, L. E. H.: Agranulocytic Angina: Failure with Pentnucleotide, ibid. **1**:205, 1935. Morris, R. A.; Miller, S., and Thacker Neville, W. S.: Agranulocytic Angina, Brit. M. J. **1**:1170, 1935. Hall, D.: Agranulocytic Angina: Four Cases Treated with Pentnucleotide, Lancet **2**:1441, 1934. Smith, G. S.: Case of Agranulocytosis Treated with Pentnucleotide, ibid. **1**:607, 1935. Ranson, F. T.: Case of Agranulocytic Angina, ibid. **1**:609, 1935.

Kracke and Parker [284] expressed the belief that the most valuable therapeutic measure is to refrain carefully from the use of drugs containing aminopyrine during the patient's illness. Minot and Castle [300] stated that the effectiveness of various therapeutic agents is difficult to estimate and that at present there is only general agreement that the patients should not be given aminopyrine during their illness.

HEMATOLOGIC TECHNIC

Of basic importance in the study of the morphology of the blood, the evaluation of therapeutic measures and the analysis of statistical data are accepted standards for normal values. Such standards, based on the careful hematologic study of 500 rigidly selected healthy persons, have been compiled by Osgood. [301] They comprise values for the erythrocyte count, hemoglobin content, hemoglobin coefficient, color, volume and saturation indexes, reticulocyte count, total and differential leukocyte counts and sedimentation rate. Persons of both sexes and of all ages from 4 to over 30 years are represented.

Schnabel [302] and others have reemphasized the value of estimation of the size of the erythrocytes and the hemoglobin content as a means of classifying anemia on an etiologic as well as on a morphologic basis. The study, in conjunction, of the number, size and hemoglobin content of the red blood cells yields an insight into the nature of anemia caused by deficiency and provides a rational basis for its treatment. [64]

Although it is generally held that determination of the iron content of the whole blood yields no more information than an accurate estimation of the hemoglobin content, Josephs, [303] studying the blood of infants, found, especially between the second and the third week of life, that the hemoglobin value calculated from the iron content is appreciably higher than that obtained by the Newcomer method. He had no explanation for this discrepancy.

There is still lacking a standardized technic for the enumeration of the platelets. Two new modifications of older procedures have been proposed during the past year. One, described by Lempert, [304] is essentially

300. Minot, George R., and Castle, W. B.: Malignant Neutropenia, in The 1935 Year Book of General Medicine, Chicago, Year Book Publishers, Inc., 1935, p. 424.

301. Osgood, E. E.: Normal Hematologic Standards, Arch. Int. Med. **56**:849 (Nov.) 1935.

302. Schnabel, T. G.: The Laboratory as an Approach to Anemic Therapy, J. Lab. & Clin. Med. **20**:714, 1935.

303. Josephs, H. W.: The Iron of the Blood: A Comparison of Values for Hemoglobin Determined by the Newcomer Method and Calculated from the Iron Content, Bull. Johns Hopkins Hosp. **56**:50, 1935.

304. Lempert, H.: A Modified Technique for the Enumeration of Blood Platelets, Lancet **1**:151, 1935.

a simplification of Kristenson's direct method and employs a white blood cell pipet and a new diluting and hemolyzing fluid. The other, a modification of Fonio's indirect method, has been described by Gradwohl.[305] By staining for thirty minutes with diluted Giemsa stain, washing in neutral distilled water and restaining for thirty minutes, he has eliminated precipitate and obtained a deeper stain of the blood platelets. It is of interest that by these two radically different procedures the same range of normal values is obtained, from 250,000 to 350,000 platelets per cubic millimeter.

There is likewise a lack of a standardized procedure for the determination of the sedimentation rate or suspension stability of the erythrocytes. Although it has been contended that the use of potassium oxalate as an anticoagulant delays the rate of sedimentation as compared to the values obtained when heparinized blood is used, Wintrobe and Landsberg[306] have shown that this is not necessarily the case. By the use of a dry mixture of 6 mg. of ammonium oxalate and 4 mg. of potassium oxalate for each 5 cc. of venous blood they eliminated any effect on the sedimentation rate as compared to that of heparinized blood. With the description of the instrument and the method employed in their studies, these authors give a chart for the correction of the sedimentation rate when alterations are due to anemia and consequent reduction of the volume of packed red cells. Another group of investigators[307] have determined that the sedimentation rate is increased both by heparin and by other anticoagulants when used dry. They found most satisfactory the use of a 3 per cent solution of sodium citrate and from 0.5 to 4.5 cc. of blood. In Europe, much more than in America, attention has been given to microsedimentation methods. Raponsky,[308] who has written extensively on this subject, summarized the disadvantages of the macromethods employing venous blood, chief among which are the inconvenience, the effect of stasis and the necessity of transferring the blood from one receptacle to another with consequent likelihood of altering the suspension stability. The usual drawbacks to the micromethods, he stated, are the danger of partial clotting, hemolysis and the difficulty of obtaining a uniform mixture of the blood with the anticoagulant. He expressed the belief that his technic, utilizing a specially constructed

305. Gradwohl, R. B. H.: A New Method of Staining Blood Platelets, J. A. M. A. **105**:1030 (Sept. 28) 1935.

306. Wintrobe, M. M., and Landsberg, J. W.: A Standardized Technique for the Blood Sedimentation Test, Am. J. M. Sc. **189**:102, 1935.

307. Greisheimer, E. M.; Hodapp, A., and Goldsworthy, E.: Effect of Anticoagulants on Sedimentation Rate, Am. J. M. Sc. **190**:775, 1935.

308. Raponsky, A. I.: Contribution à l'étude de la sédimentation sanguine: Méthodes de la sédimentation sanguine, Paris méd. **2**:461, 1934; 129, 1935.

pipet, obviates these disadvantages. Bartsch [309] advocated the micro-procedure of Langer and Schmid and found that his results with it agree well with those obtained by the Westergren method. Heimann [310] found that although the sedimentation rates determined on capillary and venous blood do not agree, the relative alterations are the same whether micro-methods or macromethods are used.

309. Bartsch, H.: Die Blutsenkungsreaktion nach der Micromethode, Deutsches Tuberk.-Bl. **9**:46, 1935.

310. Heimann, F.: Die sechsmomentige Mikrosedimentierung der roten Blutkörperchen und ihre Anwendung in Gynäkologie und Geburtshilfe, Monatschr. f. Geburtsh. u. Gynäk. **98**:266, 1935.

Book Reviews

Agents of Disease and Host Resistance. By Frederick P. Gay and others. Price, $10. Pp. 1,581, with illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1935.

This huge tome is an encyclopedic work dealing with disease from the standpoint of the causes and the part that the host plays in the disease. Realizing that this subject was too inclusive for one author, Gay has used a collaborating staff of nineteen specialists, most of whom are associated with the College of Physicians and Surgeons of Columbia University.

The book confines itself largely to principles rather than to practice and does not contain, except in rare instances, any details concerning the technic of the laboratory sciences with which it deals. An attempt has been made to have the book fall somewhere between the designation of a textbook, on the one hand, and detailed systems or monographs on the other. In this respect the work is a success, for it will give the reader all that is necessary in most instances, unless he is specifically interested in some small part of a chapter. The liberal bibliography at the end of each chapter refers to works which, for the most part, have been published within the last two decades. The book is divided into twelve parts containing sixty-five chapters. These divisions are: the general aspects of the causation, the classification and nature of disease; inanimate disease agents and tolerance; living disease agents, particularly bacteria, their morphology and physiology; infection and epidemiology; resistance and immunity; pathogenic bacteria and the diseases produced by them; pathogenic spirochetes and spirochetoses; pathogenic fungi and fungus diseases; indeterminate pathogenic forms and the diseases produced by them; animal pathogens; diseases of obscure etiology, and the practical results in the diagnosis, prevention and cure of infectious diseases. Throughout the book extensive use is made of tables. Two particularly valuable sets are that dealing with the chronology of the discovery of pathogenic agents and that dealing with the bacteriologic and immunologic tests used in the diagnosis of infectious diseases, although there are a host of other tables perhaps equally interesting and valuable.

For the most part, the findings of investigators are reviewed without concluding comments, yet in some instances the author has seen fit to express a definite opinion. For example, one finds such statements as the following: "In short, the entire hypothesis of selective localization is unfounded." When such conclusions are reached they are based on a rather careful evaluation of the material which has gone before. With the present interest in medical mycology, one will welcome the clear and concise chapter on this subject; much of the material in it represents original work of the author.

As in most books compiled by a group of authors, one finds inconsistencies; for example, the genus "Endameba" (which is incorrect) is used in the chapter dealing with pathogenic protozoa, while "Entameba" (also incorrect) is used in the chapter on the general physiology of micro-organisms. The same failure to correlate sections is noted in the chapter on chemotherapy; carbon tetrachloride is indicated for the treatment of hookworm without any reference to hexylresorcinol, which in turn is indicated as excellent treatment in the section dealing with hookworm disease. Some sections do not compare favorably with others. The chapter on animal parasites could definitely be improved in many particulars, chiefly by the inclusion of material which is omitted. For example, there are no mention of Plasmodium ovale, no discussion of the use of arsenic in amebiasis and no mention of the extensive monograph by Birkeland dealing with Diphyllobothrium, which, had it been examined, would have saved the author from the common error of indicating that fatal anemia is frequent in this type of infestation. One cannot help but wonder about the statement concerning the diagnosis of

trichiniasis, which recommends examination of the diaphragm in the region of the central tendon for larvae in the third week or later, if a diagnosis has not been established. This would be a drastic method, to say the least, in the average live human being! In the chapter dealing with chemotherapy there is no discussion of the treatment of amebiasis, although some experimental work is briefly mentioned. Another example of omission is the failure to discuss Kahn's recent work on the skin as a defensive mechanism. Since the book is well illustrated with many cuts and has many excellent color plates, it is curious that a figure so unrevealing as figure 140 should have found its way into the text.

In a work of this nature the index is, of course, important. In this work the index, which embraces nineteen pages, is well arranged, although there is some difficulty occasionally in finding titles, which should be expected. It would have been particularly advantageous to have appended an author's index.

In a book of this magnitude it is surprising that one can find so few complaints to register. That in itself should indicate that this work represents a distinct contribution to medical literature and that it will serve more or less as an encyclopedia for years to come.

Bee Venom Therapy; Bee Venom, Its Nature, and Its Effects on Arthritic and Rheumatoid Conditions. By Bodog F. Beck, M.D. Cloth. Price, $5. Pp. 238. New York: D. Appleton-Century Company, Inc., 1935.

For centuries folk-lore has continued the idea that various diseases, "rheumatism" in particular, can be cured by bee stings or by the use of bee venom. The idea has been the basis of a therapy that has been dropped and revived many times. It is Beck's belief that it has been discarded so often not because of its lack of value but because of the difficulties inherent in the use of actual bee stings. Recently (1928), bee venom has been made commercially available in ampules for ready use. Bee venom therapy has regained considerable popularity in Europe but remains practically untried in this country. The author purposes to give a detailed description of the present status of such therapy in its modern modification and to present the results obtained by foreign workers, in order that "apitherapy" may at last be taken out of the hands of the laity and placed on a scientific basis.

To this end Beck has given an extensive review of a hundred years of medical and popular literature on the healing properties of bee venom. Chapters concern the use of animal venom and of formic acid (which, the author states, is contained in the venom of ants but not in that of bees), the chemistry and the physiologic effects of bee venom and bee stings, conditions of decreased and increased sensitivity thereto and the use of apitherapy for various types of rheumatism and arthritis. It is stated that "arthritic and rheumatic subjects" possess an abnormal (pathologic) immunity to bee venom and that patients with tuberculosis, syphilis and gonorrhea are unusually sensitive thereto—a point of almost diagnostic significance.

The author accepts as practically proved the theory that "rheumatic conditions" are the result of impaired circulation. In such disorders the endings of sympathetic nerves are overstimulated and produce vasoconstriction, with anemia of the tissues, and anoxemia and suboxidation result. In time this causes the accumulation of waste products, particularly lactic acid, in articular and muscular tissues. Bee venom contains an endothelial toxin which dilates capillaries and causes their walls to become permeable to corpuscles. It exerts its beneficial influence by accelerating and intensifying circulation to tissues presumably starved for blood. It is claimed that the venom is especially successful in cases of myositis, myalgia, neuritis and early rheumatoid arthritis and that it is "almost specific for rheumatic fever and endocarditis." The results are "very good" in Bechterew's spondylitis and are also good in acute and chronic gout.

Chapters on the effects of bee stings and on the treatment should be of interest and of some practical value to general practitioners and bee-keepers. The sections on the use of bees and bee venom are, unfortunately, of more historical than scientific value, as but few of the reports are critically reviewed. Several major

deficiencies in the author's presentation are recognizable at once to any one with an intimate knowledge of the modern problem of the rheumatic diseases. From the author's continuous use of the vague terms "rheumatism and arthritis"; "arthritism caused by endocrine imbalance"; "chronic arthritis"; "arthritis deformans," and "rheumatoid heart affections," it would appear that his experience with rheumatic diseases is largely *ex bibliotheca*. His bland acceptance of the neurogenic theory and the lactic acid hypothesis puts him out of step with the great majority of recognized authorities in this field and dates his ideas to a previous medical generation. However, the reader who peruses the book with an open mind becomes affected by Beck's general optimism, is tolerant of the inadequacies of the quoted material and is ready to hear at last some new clinching evidence in favor of bee venom therapy, which is based on the author's series of cases—one series studied scientifically with adequate controls. Here the author lets his readers down completely. Not a single case of the author's is presented in detail or even in abstract. No table of his own results is given; merely the review of the writings of others and a summary of the testimonials of laymen and bee-keepers are offered. What little information is given on a plan of dosage or on the technic of administration is incomplete and poorly defined. Beck's reason for omitting any enumeration of records of his own cases is that he is pressed for information on his technic of administration, and "in order not to delay publication any longer" he "reserves the privilege of publishing my records at a later date." He states that he is convinced that the inclusion of additional reports of cases would be more disturbing than helpful. If his own records are no more adequately presented than those that he has reviewed, one is inclined to agree that they would be more disturbing than helpful. One must conclude that the author has, by this grave omission, failed completely in his purpose, that the value of bee venom is still a part of folk-lore or unscientific medical ideology and that bee venom therapy still awaits its Jenner.

Urethrography. Detailed Consideration in 154 Males. By Folke Knutsson. Acta radiologica, supplement XXVIII. Pp. 155, with 55 illustrations. 1935.

In this publication one hundred and fifty-four cases of conditions studied by means of urethrograms are analyzed and the results are corrolated with the clinical operative and pathologic findings. The conditions include strictures, urinary fistulas, and prostatic disease, both inflammatory and obstructive. In some cases the urethra was studied after operation and, interestingly, the results of prostatectomy were demonstrated.

Knutsson used iodized oil almost exclusively as his contrast medium, chiefly because of its low degree of irritation. Using a special syringe and clamp arrangement, he injected the medium and filled the urethra while the plates were being exposed, in order to visualize the posterior part of the urethra. One plate was exposed after injection of the medium in order to make possible study of the reflex contraction of the prostatic part of the urethra. Urethrograms were taken in the anteroposterior, lateral and right and left oblique positions.

In this series there were four cases of urethrovascular reflux, which the author believes can be avoided if urethrography is not done in the presence of urethral bleeding or if it does not follow too closely after sounding or cystoscopy.

The illustrations in this publication are remarkable and instructive, and the author's interpretations are accurate. The work has definite scientific value and proves that in many instances urethrograms are of distinct clinical advantage.

In criticism, the reviewer would suggest that a single contrast medium to be used in all cases is not adequate. In many instances a highly viscous medium, such as iodized K-Y jelly, is advantageous; in others a watery solution is preferable to oil. Iodized oil has the disadvantage of floating on urine and does not always give an accurate outline of the surface of the prostate adjoining the bladder.

Body Water: The Exchange of Fluids in Man. By John P. Peters. Price, $4. Pp. 405. Springfield, Ill.: Charles C. Thomas, Publisher, 1935.

The subject of the exchange of fluids in man has developed so rapidly and to such proportions that a review of it by some one who can speak with authority is badly needed. Peters is qualified to undertake such a review by his many years of study, as well as by his own many contributions in this field. Expressing the opinion that the conception of vital activity should be banished beyond the horizon of the research worker, he emphasizes the significance of physicochemical forces in the control of fluid exchange.

The subject is developed in twelve chapters. It may be considered in three parts:

The first part deals with the distribution of fluids in the body. The physicochemical principles underlying the passage of water and solutes in and out of the different compartments of the organism are presented, with special attention to the conclusions of Starling and the modification of these by later investigators. Special attention is paid to the equilibrium between hydrostatic pressure and the osmotic pressure of proteins and salts and to the permeability of biologic membranes. In spite of the fact that so much research has been carried on, a great amount of it in his laboratory, Peters feels that this part of the subject will be lacking in accuracy until better means are found for making chemical determinations of tissues and interstitial fluids.

The second part deals with the exchange of fluid between the body and its environment as this is effected through the respiratory tract and the skin. The subject of water balance receives a full discussion.

The third part, although allied to the second, deals with the kidney and its important part in the metabolism of water. The work of Richards is presented in detail, and the theory and observations of Rehberg are reviewed. In addition, the function of the isolated kidney is considered in relationship to the body as a whole.

The book is highly recommended. It is one of the most complete presentations of the subject, if not the most complete. It is well written and is accompanied by a large and well selected bibliography which will be of inestimable value to those specially interested in the field.

Disease and Destiny. By Ralph H. Major, M.D. With a preface by Logan Clendening, M.D. Price, $3.50. Pp. 338, with 47 illustrations. New York: D. Appleton-Century Company, Inc., 1936.

Major, Professor of Medicine in the University of Kansas, already known for his adventures into the field of general literature through "The Doctor Explains," now offers a volume which will appeal to every one with an interest in romance. "Disease and Destiny," like Zinsser's "Rats, Lice and History," vividly portrays the part played by disease in shaping the course of human events. The author has traveled extensively; for many years his vacations have been spent in acquiring a personal acquaintance with the settings of the events that he describes, and his studies in the original literature in medicine, embodied recently in another book, "Classic Descriptions of Disease," fit him well for the present task. It probably was a congenial task. The result will provide many a pleasant hour for the reader.

The subjects of the various chapters in the book are as follows: the black death, the plague which brought to an end the Golden Age of Pericles; typhus, which decimated many armies, including Napoleon's in Russia; "the king's evil," or scrofula; smallpox; membranous croup; "the pestilence that walketh in Darkness," or malaria; "the disease of Lazarus," or leprosy; "yellowjack," or yellow fever; "the legacy of bleeding" (hemophilia), which contributed to the downfall of the Russian Empire, and "the worst plague of all," syphilis.

La maladie de Skévos Zervos ou maladie des pêcheurs d'éponges nus. By Skévos G. Zervos. Pp. 29. Paris: J. B. Baillière et fils, 1935.

In 1903 Skévos Zervos reported his observations on a disease afflicting many of the sponge fishers of his native Calymnos. The present volume is an interesting compilation of his continued studies of a hitherto undescribed disease. The condition was first named the disease of the naked sponge fishers; but, since it has been observed in other persons, the author ingenuously explains, it is now called the *maladie de Skévos Zervos.* This malady is characterized by a localized lesion which suppurates and becomes gangrenous and is associated with chills, fever, erythema, anorexia and prostration. The mortality is almost nil; but the morbidity is said to be high. The etiologic agent appears to be a venom produced by an actinian, a variety of sea-anemone, which Skévos Zervos says is parasitic on sponges in certain waters. The author states that the venom, which is most virulent in August, is introduced by way of scratches in the victim's skin. That the actinian is virulent and that the virulence is well known to the Aegean islander is indicated by the custom of feeding these anemones to cats and dogs in order to poison them. The animals die of convulsions directly afterward. It appears that this malady is a disease sui generis, due to some secretory product of the sea-anemones of that region and probably related to the sting of the giant medusa, or man-of-war, which, however, is much more benign.

Archiv und Atlas der normalen und pathologischen Anatomie in typischen Röntgenbildern: Die theoretischen Grundlagen und Möglichkeiten der röntgendiagnostischen Weichteiluntersuchung. By Dr. Adolf Zuppinger. Paper. Price, 16 marks; bound, 18 marks. Pp. 99, with 46 illustrations. Leipzig: Georg Thieme, 1935.

As the title indicates, this brochure is devoted to a discussion of the theoretical bases and potentialities of roentgen depiction of soft tissues. Essentially, then, it gives an exposition of principles rather than a specific description of practical technics. It deals with the physical, physiologic and geometric factors which enter into roentgenography of soft parts and thus suggests methods by which favoring elements can be fostered and hindering elements can be combated. The reader who is confident in his understanding of the German language and is familiar with mathematical, geometric and trigonometrical formulas will find the book worth while, but the roentgenologist who has forgotten his academic training or the technician who is looking for ready-made technics is likely to find it disappointing.

Zweite Internationale Kropfkonferenz. Edited by Dr. Otto Stiner. Price, 25 marks. Pp. 698, with 128 illustrations and many tables. Bern: Hans Huber, 1935.

This volume contains a report of the proceedings of the Second International Goiter Conference held in Bern between Aug. 10 and 12, 1933. Obviously the program was carefully considered. It was divided, like Gaul, into three parts: first, hyperthyroid states received consideration; then were reported newer points of view regarding the cause of endemic goiter, and finally malignant diseases of the thyroid were discussed. A large group of investigators interested in goiter foregathered, and the list of those who presented papers is truly international. As published the papers are in French, German, Italian and English; all are short and give in abstract form the various readers' views. One can skim through the volume and pick out here and there almost anything one may wish to know concerning thyroid disorders. On the whole, the book is a convenient reference work. Perhaps it is more important for the larger medical libraries than for individual physicians to own this volume, although any one interested in goiter problems may wish to refer to it and will be glad to know of its publication.

Localized Rarefying Conditions of Bone. By E. S. J. King. Price, $7.50. Pp. 400, with 70 illustrations. Baltimore: William Wood & Company, 1935.

This monograph, as the preface states, comprises material submitted for the Jacksonian Prize of the Royal College of Surgeons in 1933 and entitled "The Pathology, Diagnosis and Treatment of Localized Rarefying Changes in Bone as Exemplified by Legg-Perthes' Disease, Osgood-Schlatter's Disease, Kümmell's Disease and Related Conditions." The special material is preceded by eighty-four pages of general considerations—bone formation and physiology, pathology, roentgenology and so on. The special sections give the most intricate details of the subject of osteochondritis, there being separate sections, each with an extensive bibliography, on each bone. The whole work is intensive and scholarly, obviously of great importance to the specialist.

The A B C of the Endocrines. By Jennie Gregory, M.S. Price, $3. Pp. 126, with illustrations. Baltimore: Williams & Wilkins Company, 1935.

By means of a series of ingenious diagrams and sketches the author attempts to present a résumé of the present knowledge of endocrinology. The general style of this publication is sufficiently like that of a Mother Goose book to evoke a smile at first, but one soon realizes that this is no laughing matter at all and that the author has presented a sound, scholarly and immensely useful book of reference. However, it is unfortunate that many of the diagrams must be a little hypothetic, in view of the rapidly changing status of certain phases of the subject.

Ueber Erkrankungen des arteriellen Systems. By F. Curtius; R. Engel; H. Marx, and R. Siebeck. Price, 3.50 marks. Pp. 102. Leipzig: Georg Thieme, 1935.

This volume contains a series of five lectures for general practitioners on the subject of arterial disease, especially hypertension, The discussion is adequate, well written and thoroughly in accord with modern practice, but nothing that is particularly new is brought out.

Studien zur Pathogenese. By Viktor von Wiezsäcker. Price, 3.50 marks. Pp. 89. Leipzig: Georg Thieme, 1935.

Brief articles on certain psychiatric angles of disease are given here, but the material is not discussed in any systematic manner.

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